

The following table displays the inclusion and exclusion criteria for both HEE studies.

Table 21: Eligibility Criteria for MHEE Studies

Inclusion Criteria	Exclusion Criteria
1. Prior to any study-specific procedures being performed, the subject voluntarily signed an informed consent form (ICF) and any privacy statement/authorization form required by the region in which the subject participated, after having its contents fully explained and all questions answered. An Institutional Review Board/Independent Ethics Committee approved the ICFs.	1. Any condition that may have required surgery during the course of the study.
2. Subjects successfully completed the Phase 3 Study T-EE04-084 or Study T-EE04-085 and had endoscopically proven healed EE.	2. Use of prescription or non-prescription PPIs, H ₂ RAs, or sucralfate throughout the study. 3. Chronic use (>12 doses per month) of non-steroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase-2 NSAIDs throughout the study; however, low dose aspirin up to 325 mg per day was allowed.
3. All female subjects agreed to continue use of a double-barrier method of birth control. Oral, injectable, or patch contraceptives may have been used as one method if the subject had been taking them for greater than 3 months duration at the Screening Visit. Subjects who had a bilateral tubal ligation, hysterectomy, or were postmenopausal (the absence of menses for 1-2 years with a follicle-stimulating hormone level $\geq$ 40 IU/L or absence of menses for $>$ 2 years) were not required to use birth control.	4. Use of antacids [except for study supplied Gelsil (North American sites) or a similar equivalent approved antacid (sites outside of North America)] throughout the study. 5. Subjects using drugs with significant anticholinergic effects such as tricyclics who could not stay on a stable dose throughout the study. 6. Use of misoprostol or prokinetics throughout the study. 7. Need for continuous anticoagulant therapy. 8. Evidence of uncontrolled systemic disease. 9. Subjects who, in the opinion of the investigator, were unable to comply with the requirements of the study or were unsuitable for any reason. 10. Subjects who participated in any other maintenance of healed EE dexlansoprazole MR study.

Source: Table 2.7.3.3.c., p.38, Module 2.7.3., NDA 22-287

6.2.1.3 Efficacy Endpoints

An overview of the endpoints for the two studies is presented below:

Primary Efficacy Variable

- The percentage of subjects who maintained healed EE for 6 months, as assessed by endoscopy.

The crude rate analysis at Month 6 of the primary efficacy variable is considered the primary analysis. The crude percentage of subjects who maintained healed EE per endoscopy for each of Months 1, 3, and 6, out of those subjects who were ITT for the primary endpoint were calculated for each treatment group. The intervals for Months 1, 3 and 6 were defined as Days 2 to 35, Days 36 to 105, and Days 106 to 195, respectively. Subjects with an endoscopy showing recurrence anywhere in the interval are considered as recurred for the visit. Those subjects who did not have a recurrence of EE and did not complete the study were included in the analysis according

to their last endoscopy date. If the last endoscopy that showed no recurrence was during the predefined visit window (Days 21 to 35 for Month 1, Days 75 to 105 for Month 3, and Days 165 to 195 for Month 6), the subjects were considered maintained during that visit but conservatively included for any later visits as having recurrence. Subjects who prematurely discontinued with the final endoscopy showing no recurrence in the early part of the interval for Month 1, 3, or 6 (i.e., before predefined visit windows described above) cannot be considered to have evidence of no recurrence for that visit (egg, at Day 55 for Month 3). Thus, those subjects are conservatively assumed as having recurred for that visit. Subjects who had a recurrence after the visit window for Month 6 were still considered to have recurred at Month 6.

The crude rates calculated for the primary efficacy endpoint are thus very conservative as subjects who prematurely discontinued with their last endoscopy showing no recurrence are assumed as having recurred as described above.

Medical Officer Comments:

The reviewer believes that the chosen primary endpoint is clinically meaningful and provides an acceptable method for demonstrating efficacy for the proposed indication.

Secondary Efficacy Variables

- The percentage of days with neither daytime nor nighttime heartburn (24-hour heartburn-free days) during treatment, as assessed by daily diary.
- The percentage of nights without heartburn during treatment, as assessed by daily diary.

Additional Efficacy Variables

- The percentage of subjects who maintained healed EE at Month 1 or Month 3, as assessed by endoscopy.
- Time to recurrence among those who experienced a recurrence.
- The mean severity of daytime and nighttime heartburn during all of treatment, as assessed by daily diary.
- The mean severity of nighttime heartburn during all of treatment, as assessed by daily diary.
- The percentage of days without rescue medication during all of treatment, as assessed by daily diary.

6.2.1.4 Statistical Considerations

For each efficacy variable, the overall level of significance was 0.0025 and the comparisons of each dexlansoprazole MR dose to placebo used Hochberg's method to control the overall significance rates with the multiple comparisons. Comparisons between the 2 dexlansoprazole MR doses were made for each efficacy variable with no adjustment to the 0.0025 level of significance, since this comparison was not the primary assessment in this study.

The secondary efficacy endpoints, (1) the percentage of 24-hour days without heartburn during

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treatment and (2) the percentage of nights without heartburn during treatment were summarized by treatment group, and comparisons between dexlansoprazole MR and placebo for each variable were made with Wilcoxon rank-sum tests. For each dexlansoprazole MR dose that was found to be superior to placebo for the primary efficacy variable, evaluation of the first secondary variable was performed. Evaluation of the second secondary variable was then performed only for the dexlansoprazole MR doses that were superior to placebo for the first secondary efficacy variable.

Medical Officer Comments:

The sponsor chose a large number of secondary endpoints for study; however, they have designated two of these as “secondary,” while the others are considered “additional.” Since a hierarchical testing strategy was employed for the “secondary” endpoints and they could potentially be included in labeling, the reviewer has renamed these as “key secondary endpoints.” However, the sponsor-designated “additional endpoints” will not be eligible for inclusion in labeling. Moreover, the reviewer believes that these endpoints provide a relatively insignificant contribution toward demonstrating the efficacy of the product when compared to the primary and key secondary efficacy findings. For these reasons, the reviewer has chosen not to present a written review of these endpoints and will instead focus on presenting a detailed review of the primary and “key secondary” efficacy data.

The sponsor appears to have designed these studies to maintain acceptable Type I error control for the multiple comparisons between different dex doses for the primary and key secondary endpoints. However, final determination of the statistical soundness of the sponsor’s methods will be made by the Biostatistics reviewers for this application. Please see their respective reviews for a more detailed analysis.

6.2.2 Demographics/Baseline Characteristics

All of the following demographic information is presented and discussed as an integrated analysis for the two MHEE studies (Study T-EE05-135 and Study T-EE04-086).

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The following table presents the demographics for the two studies for MHEE.

Table 22: Demographics for MHEE Studies

	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
Gender: n (%)					
Male	142 (49.8)	69 (50.4)	153 (49.0)	82 (53.9)	446 (50.3)
Female	143 (50.2)	68 (49.6)	159 (51.0)	70 (46.1)	440 (49.7)
Ethnicity: n (%)					
Hispanic or Latino	35 (12.3)	21 (15.3)	38 (12.2)	14 (9.2)	108 (12.2)
Not Hispanic or Latino	250 (87.7)	116 (84.7)	274 (87.8)	138 (90.8)	778 (87.8)
Race: n (%)					
American Indian/Alaska Native	2 (0.7)	0	6 (1.9)	1 (0.7)	9 (1.0)
Asian	5 (1.8)	3 (2.2)	6 (1.9)	0	14 (1.6)
Black	15 (5.3)	5 (3.6)	28 (9.0)	11 (7.2)	59 (6.7)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.3)	0	1 (0.1)
White	260 (91.2)	125 (91.2)	267 (85.6)	136 (89.5)	788 (88.9)
Multiracial	2 (0.7)	4 (2.9)	4 (1.3)	4 (2.6)	14 (1.6)
Age (yr)#					
<45: n (%)	96 (33.7)	52 (38.0)	111 (35.6)	56 (36.8)	315 (35.6)
45-65: n (%)	164 (57.5)	74 (54.0)	173 (55.4)	81 (53.3)	492 (55.5)
≥65: n (%)	25 (8.8)	11 (8.0)	28 (9.0)	15 (9.9)	79 (8.9)
Mean±SD	48.9±12.90	47.3±13.14	48.9±12.21	48.8±13.76	48.6±12.84
Median	49.0	50.0	49.0	51.0	49.0
Min-Max	18-84	21-85	20-81	18-83	18-85
Weight (kg)#					
Mean±SD	87.2±18.49	89.1±19.07	90.1±19.55	90.2±19.72	89.0±19.18
Median	86.3	88.5	88.5	88.1	87.6
Min-Max	46-149	45-165	48-186	41-156	41-186
Height (cm)&					
N	284	137	308	152	881
Mean±SD	169.9±10.35	170.2±9.83	170.1±10.36	171.6±10.08	170.3±10.23
Median	170.2	170.2	168.9	172.7	170.2
Min-Max	135-193	150-193	127-193	152-193	127-193
BMI (kg/m ²)=&					
<25: n (%)	48 (16.8)	22 (16.1)	45 (14.4)	24 (15.8)	139 (15.7)
25-30: n (%)	111 (38.9)	48 (35.0)	105 (33.7)	58 (38.2)	322 (36.3)
≥30: n (%)	125 (43.9)	67 (48.9)	158 (50.6)	70 (46.1)	420 (47.4)
Missing	1 (0.4)	0	4 (1.3)	0	5 (0.6)
N	284	137	308	152	881
Mean±SD	30.2±6.08	30.8±6.57	31.3±7.05	30.6±6.15	30.7±6.53
Median	29.5	29.9	30.0	29.5	29.7
Min-Max	19-58	18-63	19-81	17-49	17-81

Source: Table 2.7.3.3.d., p. 40, Module 2.3.3, NDA 22-287

As can be seen from the table above, approximately half of ITT subjects were male (50.3%), the majority were White (88.9%), not Hispanic or Latino (87.8%), ≥45 years of age (64.4%), and had a BMI ≥25 kg/m² (83.7%). No statistically significant differences were observed among treatment groups for any demographic characteristic.

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Medical Officer Comments:

The above demographics are of necessity consistent with those of the patient population that would require and receive treatment for the maintenance of erosive esophagitis.

The following table presents the social history covariates for the patients enrolled in the two MHEE studies.

Table 23: Social History for Subjects in MHEE Studies

Variable	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
Alcohol Use					
Drinker	156 (55)	63 (46)	178 (57)	80 (53)	477 (54)
Non-/Ex-drinker	129 (45)	74 (54)	134 (43)	72 (47)	409 (46)
Smoking Status					
Smoker	65 (23)	37 (27)	77 (25)	48 (32)	227 (26)
Non-/Ex-smoker	220 (77)	100 (73)	235 (75)	104 (68)	659 (74)
Caffeine Use					
Caffeine User	227 (80)	107 (78)	253 (81)	133 (88)	720 (81)
Non-caffeine User	58 (20)	30 (22)	59 (19)	19 (13)	166 (19)

Source: Table 2.7.3.3.e., p. 41, Module 2.7.3, NDA 22-287

More than half of the subjects used alcohol, the majority of subjects were non-/ex-smokers, and the majority used caffeine. No statistically significant differences were observed among treatment groups for any of these characteristics.

Medical Officer Comments:

Use of any of these substances is known to worsen gastroesophageal reflux and could potentially have confounded the study results. However, it appears that use of these substances was well-balanced among the study drug and active control treatment arms.

The following table shows the baseline LA Grade for subjects in the MHEE studies.

Table 24: Baseline LA Grade for MHEE Studies

LA Grade	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
A	107 (38)	51 (37)	113 (36)	54 (36)	325 (37)
B	105 (37)	46 (34)	118 (38)	58 (38)	327 (37)
C	62 (22)	30 (22)	70 (22)	32 (21)	194 (22)
D	11 (4)	10 (7)	11 (4)	3 (5)	40 (5)

Source: Table 2.7.3.3.f., p.42, Module 2.7.3, NDA 22-287

Seventy-four percent of subjects were LA Grade A or B, and 26% were LA Grade C or D prior to treatment in the healing of EE studies. The percentages of subjects in each classification grade were similar among all treatment groups.

Medical Officer Comments:

The proportions above are consistent with those seen in the general population with erosive esophagitis.

The following table shows the duration of treatment from the HEE studies for each patient group enrolled in the MHEE studies.

Table 25: Duration of Treatment from HEE Studies

Duration of Treatment	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
4 weeks	238 (83.5)	102 (74.5)	260 (83.3)	142 (93.4)	742 (83.7)
8 weeks	46 (16.1)	35 (25.5)	52 (16.7)	10 (6.6)	143 (16.1)
Missing	1 (0.4)	0	0	0	1 (0.1)

Source: Table 2.7.3.3.g., p.43, Module 2.7.3, NDA 22-287

The majority of subjects had endoscopically proven healed EE at 4 weeks of treatment in the healing of EE studies. There was an imbalance in the percentage of subjects with healed EE after 4 weeks of treatment in the healing of EE studies across the dexlansoprazole MR doses (p=0.002). A greater percentage of subjects in the higher dexlansoprazole MR dose groups (60 mg and 90 mg) had 4 weeks of treatment in the healing of EE studies because a greater percentage of subjects with only 4 weeks of treatment enrolled in Study T-EE04-086, which included these higher doses. This was due to rapid enrollment into Study T-EE04-086 with subjects who were healed by Week 4 in the previous EE healing study, before subjects who required 8 weeks of dosing to heal were able to enroll. This imbalance also occurred in Study T-EE05-135; however, enrollment was less rapid and, therefore, a greater number of subjects who required 8 weeks of treatment to heal were able to enter the maintenance study. Therefore, more subjects who were healed by Week 4 in the healing of EE studies were enrolled in Study T-EE04-086 compared with Study T-EE05-135.

Medical Officer Comments:

Since the primary endpoint for this indication is “the percentage of subjects who maintained healed EE for 6 months,” the imbalance seen in patients on higher doses of dex who achieved healing by Week 4 vs. Week 8 in the HEE studies does not compromise the evaluation of the product’s efficacy for the proposed indication. Whether patients achieve healing by Week 4 or Week 8, they would still need to maintain healing for the entire 6-month period. In fact, maintenance of healing for 22 weeks rather than 18 weeks would be more difficult to achieve, so the imbalance discussed above would most likely make it more difficult to demonstrate efficacy over placebo.

(b) (4) (dexlansoprazole)

The following table demonstrates the previous treatment assignment from the HEE studies for each treatment group in the MHEE studies.

Table 26: Previous Treatment from HEE Studies

Previous Treatment	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=151)	
Dexlansoprazole MR 60 mg QD	89 (31.2)	52 (38.0)	100 (32.1)	50 (32.9)	291 (32.8)
Dexlansoprazole MR 90 mg QD	108 (37.9)	44 (32.1)	107 (34.3)	57 (37.5)	316 (35.7)
Lansoprazole 30 mg QD	83 (30.9)	41 (29.9)	105 (33.7)	45 (29.6)	279 (31.5)

Source: Table 2.7.3.3.h., p.43, Module 2.7.3, NDA 22-287

The distribution of subjects by previous treatment in the healing of EE studies (dexlansoprazole MR 60 mg QD or 90 mg QD or lansoprazole 30 mg QD) was similar across each maintenance of healed EE treatment group (placebo and dexlansoprazole MR 30 mg QD, 60 mg QD, and 90 mg QD).

Other variables which were assessed for patients who enrolled in the MHEE studies included:

- Baseline number of days with daytime/nighttime heartburn and baseline number of days with nighttime heartburn, where the mean number of days between treatment groups showed a statistically significant difference for both variables.
- Baseline mean severity of daytime/nighttime heartburn and baseline mean severity of nighttime heartburn, both of which were well-balanced among the treatment groups.
- Baseline number of days with daytime/nighttime rescue medication use, which was well-balanced among the treatment groups.
- Day -1 GERD symptoms investigator assessment, which was well-balanced among the treatment groups.
- Day -1 symptom severity and quality-of-life questionnaire results, which were well-balanced among the treatment groups, with the exception of a statistically significant difference among the treatment groups for the specific symptoms of nausea/vomiting (higher symptom scores seen in placebo patients).

Medical Officer Comments:

Although statistically significant differences were seen between treatment groups for some of the variables discussed above, the reviewer notes that these differences are relatively small in magnitude and/or of limited clinical relevance. As such, the reviewer does not believe that the differences seen compromise the evaluation of the product's efficacy for this indication.

6.2.3 Drug Exposure/Compliance/Patient Disposition

The following table presents the drug exposure for patients enrolled in the MHEE studies.

Table 27: Study Drug Exposure for MHEE Studies

	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
Total Time on Study Drug					
1 day - <3 weeks	46 (16)	7 (5)	10 (3)	10 (7)	73 (8)
3 weeks - <8 weeks	175 (61)	24 (18)	44 (14)	24 (16)	267 (30)
8 weeks - <12 weeks	4 (1)	2 (1)	13 (4)	2 (1)	21 (2)
12 weeks - <16 weeks	18 (6)	13 (9)	27 (9)	9 (6)	67 (8)
16 weeks - <20 weeks	0	0	1 (<1)	3 (2)	4 (<1)
20 weeks - <24 weeks	3 (1)	2 (1)	18 (6)	9 (6)	32 (4)
≥24 weeks	39 (14)	89 (65)	199 (64)	95 (63)	422 (48)
Mean±SD	53.1±55.08	135.6±65.88	140.0±61.13	134.9±63.57	110.5±72.19
Min-Max	1-198	1-201	1-220	1-203	1-220
Cumulative Time on Study Drug					
≥1 day	285 (100)	137 (100)	312 (100)	152 (100)	886 (100)
≥3 weeks	239 (84)	130 (95)	302 (97)	142 (93)	813 (92)
≥8 weeks	64 (22)	106 (77)	258 (83)	118 (78)	546 (62)
≥12 weeks	60 (21)	104 (76)	245 (79)	116 (76)	525 (59)
≥16 weeks	42 (15)	91 (66)	218 (70)	107 (70)	458 (52)
≥20 weeks	42 (15)	91 (66)	217 (70)	104 (68)	454 (51)
≥24 weeks	39 (14)	89 (65)	199 (64)	95 (63)	422 (48)

Source: Table 2.7.3.3.a., p.36, Module 2.7.3, NDA 22-287

In the integrated analysis, study drug exposure, as exhibited by the mean total days on study drug in each treatment group, was similar across the dexlansoprazole MR treatment groups and was much lower in the placebo treatment group because of the high rate of premature discontinuation among placebo subjects due to early recurrence of EE.

Medical Officer Comments:

The imbalance between dex and placebo for total time on study drug and cumulative time on study drug is expected given the high rate of premature discontinuation among placebo subjects. This is not unexpected given the natural history of untreated erosive esophagitis and indirectly supports the efficacy of the study drug.

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(b) (4) (dexlansoprazole)

The following table presents the study drug and patient diary compliance for the MHEE studies.

Table 28: Study Drug Compliance for MHEE Studies

Study Drug Compliance	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
<50%	5 (2)	0	1 (<1)	0	6 (<1)
50%-<80%	10 (4)	3 (2)	11 (4)	7 (5)	31 (3)
80%-<90%	14 (5)	9 (7)	21 (7)	6 (4)	50 (6)
≥90%	256 (90)	125 (91)	279 (89)	139 (91)	799 (90)
Mean (SD)	95.8 (10.29)	96.8 (5.43)	96.4 (7.43)	97.0 (6.34)	96.4 (8.06)
Median	100.0	99.0	99.4	100.0	99.8
Min-Max	30-100	71-100	30-100	66-100	30-100

Percentage of Expected Entries*	Treatment Group n (%)				All ITT Subjects (N=886)
	Placebo (N=285)	Dexlansoprazole MR			
		30 mg QD (N=137)	60 mg QD (N=312)	90 mg QD (N=152)	
<50%	20 (7)	16 (12)	29 (9)	13 (9)	78 (9)
50%-<80%	30 (11)	6 (4)	38 (12)	28 (18)	102 (12)
80%-<90%	31 (11)	5 (4)	23 (7)	18 (12)	77 (9)
≥90%	193 (68)	105 (77)	214 (69)	88 (58)	600 (68)
N	274	132	304	147	857
Mean (SD)	87.7 (18.69)	88.1 (21.61)	86.1 (21.79)	84.4 (20.22)	86.7 (20.55)
Median	96.3	97.8	97.1	94.8	96.4
Min-Max	3-100	15-100	1-100	16-100	1-100
Percentage of Days With at Least One Daytime or Nighttime Diary Entry					
<50%	13 (5)	14 (10)	23 (7)	11 (7)	61 (7)
50%-<80%	30 (11)	7 (5)	37 (12)	22 (14)	96 (11)
80%-<90%	22 (8)	4 (3)	18 (6)	16 (11)	60 (7)
≥90%	209 (73)	107 (78)	226 (72)	98 (64)	640 (72)
N	274	132	304	147	857
Mean (SD)	89.9 (17.37)	89.1 (21.29)	88.1 (20.60)	87.6 (18.15)	88.8 (19.31)
Median	96.4	98.9	98.2	96.6	97.1
Min-Max	4-100	16-100	3-100	20-100	3-100

Source: Tables 2.7.3.3.p., 2.7.3.3.q., p.52-53, Module 2.7.3, NDA 22-287

In the integrated analysis, the majority of subjects (90%) were ≥ 90% compliant with study drug use during the studies. Study drug compliance (mean percent compliance) was similar across the treatment groups.

The majority of subjects (68%) completed ≥90% of expected diary entries. Diary compliance (mean percent compliance) was similar across the treatment groups. Approximately 66% of subjects used paper diaries during the studies and the others used personal digit assistant (PDA) diaries.

Medical Officer Comments:

The use of PDA diaries is preferred when collecting daily patient-reported outcome (PRO) data. Since some patients will undoubtedly forget to enter data on some days, they will be attempting to recall symptoms that occurred days or weeks ago. This introduces

significant recall bias which can not be accounted for when paper diaries are used. In contrast, PDA diaries allow for confirmation of the patient's daily symptom log.

The following table depicts the patient disposition for the MHEE studies.

Table 29: Patient Disposition for MHEE Studies

Primary Reason for Discontinuation:	Treatment Group n (%)				All Subjects (N=896)
	Placebo (N=287)	Dexlansoprazole MR			
		30 mg QD (N=140)	60 mg QD (N=317)	90 mg QD (N=152)	
Total Subjects Prematurely Discontinued	245 (85)	48 (34)	103 (32)*	49 (32)	445 (50)
Other	177 (62)	28 (20)	47 (15)*	28 (18)	280 (31)
Relapse of EE	154 (54)	25 (18)	35 (11)	12 (8)	226 (25)
Possible Barrett's esophagus	3 (1)	1 (<1)	4 (1)	8 (5)	16 (2)
Therapeutic failure	17 (6)	0	4 (1)	3 (2)	24 (3)
Noncompliance	2 (<1)	0	1 (<1)	2 (1)	5 (<1)
Subject request/subject unavailable	1 (<1)	0	3 (<1)	2 (1)	6 (<1)
Esophageal stricture	0	0	0	1 (<1)	1 (<1)
Pregnancy	0	2 (1)	0	0	2 (<1)
Withdrew Consent	37 (13)	12 (9)	34 (11)	8 (5)	91 (10)
Adverse Event	21 (7)	3 (2)	12 (4)	9 (6)	45 (5)
Lost to Follow-up	9 (3)	5 (4)	9 (3)	4 (3)	27 (3)
Protocol Violation	0	0	1 (<1)	0	1 (<1)
Did Not Meet Inclusion/Exclusion Criteria	1 (<1)	0	0	0	1 (<1)

Source: Table 2.7.3.3.o., p.51, Module 2.7.3, NDA 22-287

In the individual studies, both dexlansoprazole MR doses had statistically significantly fewer subjects prematurely discontinued for any reason compared to the placebo group. Significantly more placebo subjects discontinued for "Other" reasons, which were primarily relapse of EE. In the integrated analysis, the statistical test between the dexlansoprazole MR 60-mg QD and placebo treatment groups was statistically significant both overall and for subjects with reasons of "Other," similar to results in each study. There was a reverse trend with dexlansoprazole MR dose in subjects whose reason for premature discontinuation was categorized as "Relapse of EE," with 18%, 11%, and 8% of subjects in the dexlansoprazole MR 30-mg QD, 60-mg QD, and 90-mg QD treatment groups, respectively.

Medical Officer Comments:

The imbalance noted above between the placebo group and the dex groups for premature discontinuations is not unexpected given the natural history of untreated EE, and indirectly supports the efficacy of the study drug.

6.2.4 Analysis of Primary Endpoint

As discussed in Section 6.2.1.3 above, the primary endpoint for both MHEE studies was the percentage of subjects with maintained healing of EE at 6 months.

As prespecified in the protocol and original statistical analysis plan for each of Study T-EE05-135 and T-EE04-086, the primary analysis for the primary efficacy endpoint was based on time-to-event methods (life table), and the crude rate analysis was considered as supportive. Following a request from the Food and Drug Administration at the Pre-NDA meeting on 1 October 2007, the primary analysis for the primary endpoint was changed to a crude rate analysis that was prespecified in the original statistical analysis plan (SAP) and the analysis based on time-to-event methods is now considered as supportive.

Efficacy analyses were performed on the appropriate ITT population. Subjects who had endoscopically proven EE were randomized in Study T-EE04-084 or Study T-EE04-085, were healed and did not have a gap in dosing >7 days before entering the maintenance study (T-EE05-135 or T-EE04-086) were included in the ITT population. Subjects who were ITT and also had ≥ 1 endoscopy in the maintenance study were included for the primary analysis (crude rate analysis) of the primary efficacy endpoint of the maintenance of healed EE (ITT primary subjects).

Those subjects who did not have a recurrence of EE and did not complete the study were included in the analysis according to their last endoscopy date. If the last endoscopy that showed no recurrence was during the predefined visit window (Days 21 to 35 for Month 1, Days 75 to 105 for Month 3, and Days 165 to 195 for Month 6), the subjects were considered maintained during that visit but conservatively included for any later visits as having recurrence. Subjects who prematurely discontinued with the final endoscopy showing no recurrence in the early part of the interval for Month 1, 3, or 6 (i.e., before predefined visit windows described above) cannot be considered to have evidence of no recurrence for that visit (egg, at Day 55 for Month 3).

Thus, those subjects are conservatively assumed as having recurred for that visit. Subjects who had a recurrence after the visit window for Month 6 were still considered to have recurred at Month 6. Thus, the crude rates calculated for the primary efficacy endpoint are very conservative as subjects who prematurely discontinued with their last endoscopy showing no recurrence are assumed as having recurred as described above. Pairwise comparisons between treatment groups of the percentages at Months 1, 3, and 6 were made with Fisher's exact tests.

The time-to-event analysis of the primary efficacy endpoint is supportive. The cumulative maintenance of healed EE rates and 95% confidence intervals at Month 1, Month 3, and Month 6 were also calculated for each treatment group using the life-table method. The intervals for Months 1, 3, and 6 are defined the same as for the crude rate analysis. Comparisons between the maintenance function for each dexlansoprazole MR dose and placebo were made using log-rank tests. For both the maintenance rates by the life-table method and the log-rank tests, those subjects who did not have a recurrence of EE and did not complete the study were censored according to their last endoscopy date. If the endoscopy showing no recurrence was within the predefined visit window (Days 21 to 35 for Month 1, Days 75 to 105 for Month 3, and Days 165 to 195 for Month 6), the subjects were censored at the beginning of the next interval. Otherwise, the subjects were censored the day after the endoscopy showing no recurrence. Subjects who had a recurrence after the final cut-off (Day 195) were still considered to have recurred at Month 6 (Day 195). The subjects who completed the study and did not have recurrence of EE were

(b) (4) (dexlansoprazole)

censored at Month 6.

Medical Officer Comments:

This endpoint is consistent with primary endpoints for this indication for other PPIs. The methods described above for the primary and supportive analysis for this primary endpoint appear acceptable.

The results for the primary endpoint will be presented for each individual study first; an integrated analysis will then be examined to determine whether pooling of the studies confirms the results seen in the two individual studies for the 60 mg daily dex dose. (Since the 30 mg and 90 mg doses were only evaluated in one study each for this indication, no integrated analysis can be performed for these doses.)

The following table presents the results for Study -135 for the primary endpoint.

Table 30: Primary Efficacy Endpoint Results for Study -135

	Dexlansoprazole MR		p-value	
	Placebo	30 mg QD	60 mg QD	Dex MR 30 mg QD vs placebo vs placebo Dex MR 60 mg QD vs placebo Dex MR 30 mg QD vs Dex MR 60 mg QD
Primary Endpoint				
Primary Crude Rates: ITT Primary Subjects				
	(N=119)	(N=125)	(b) (4)	(b) (4) (b) (4)
	% (95% CI)	% (95% CI)		
Month 1 ^{a,h}	42.9 (33.8, 52.3)	88.8 (81.9, 93.7)		≤0.00001†
Month 3 ^{a,h}	22.7 (15.5, 31.3)	74.4 (65.8, 81.8)		≤0.00001†
Month 6 ^{a,h,c}	14.3 (8.5, 21.9)	66.4 (57.4, 74.6)		≤0.00001†
Supportive Life-Table Rates: ITT Subjects				
	(N=145)	(N=137)		≤0.00001†
Month 1 ^d	49.0 (40.5, 57.6)	89.3 (84.0, 94.6)		
Month 3 ^d	34.1 (25.3, 42.9)	80.2 (73.2, 87.2)		
Month 6 ^{c,d}	27.2 (18.3, 36.0)	74.9 (67.2, 82.6)		

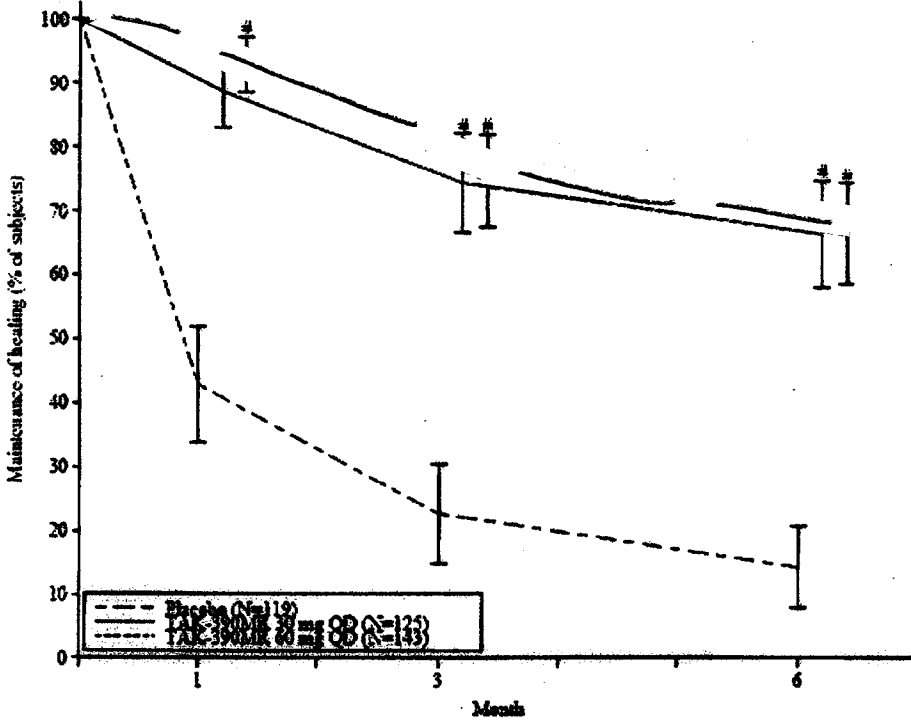
Source: Table 2.7.3.2.b., p.26, Module 2.7.3, NDA 22-287

In Study T-EE05-135, dexlansoprazole MR 30 mg and 60 mg QD were statistically significantly superior to placebo in maintaining healed EE, with 66.4% of subjects in each of the dexlansoprazole MR 30-mg QD and 60-mg QD treatment groups demonstrating maintenance of completely healed EE for 6 months compared to 14.3% in the placebo group using the crude rates in which subjects that prematurely discontinued without evidence of recurrence are considered to have recurrence of EE. When supportive life-table methods are used, which account for the subjects who prematurely discontinued by censoring, the rates are 74.9% and 82.5% for the dexlansoprazole MR 30-mg and 60-mg treatment groups compared to 27.2% for the placebo group.

(b) (4) dexlansoprazole)

The following figure demonstrates the rates over time of healing in the different treatment groups for Study -135.

Figure 4: Primary Crude Rates for MHEE (Study -135)



b(4)

Source: Figure 2.7.3.2.b., p.27, Module 2.7.3, NDA 22-287

Medical Officer Comments:

The efficacy of dexlansoprazole 30 mg and 60 mg over placebo is clearly demonstrated in the above study, and the reviewer believes this difference to be clinically relevant. There is no difference seen, however, between the 30 mg and 60 mg dex doses.

(b) (4) dexlansoprazole)

The following table presents the results from Study -086, which compared dexlansoprazole 60 mg and 90 mg daily doses to placebo.

Table 31: Primary Efficacy Endpoint Results for Study -086

	Placebo	Dexlansoprazole MR		p-value	
		60 mg QD	90 mg QD	Dex MR 60 mg QD vs placebo	Dex MR 90 mg QD vs placebo
Primary Endpoint					
Primary Crude Rates: ITT Primary Subjects					
	(N=112)	(N=152)	(N=138)		
	% (95% CI)	% (95% CI)	% (95% CI)		
Month 1 ^{a,b}	30.4 (22.0, 39.8)	(b) (4)			
Month 3 ^{a,b}	16.1 (9.8, 24.2)				
Month 6 ^{a,b,c}	14.3 (8.4, 22.2)				
Supportive Life-Table Rates: ITT Subj					
	(N=140)				
Month 1 ^d	38.6 (30.1, 47.2)				
Month 3 ^d	27.2 (18.6, 35.9)				
Month 6 ^d	25.7 (17.0, 34.4)				

Source: Table 2.7.3.2.d., p.32, Module 2.7.3, NDA 22-287

In Study T-EE04-086, dexlansoprazole MR 60 mg and 90 mg QD were statistically significantly superior to placebo in maintaining healed EE, with (b) (4) and (b) (4) of subjects in the dexlansoprazole MR 60-mg QD and 90-mg QD treatment groups maintaining complete healing of EE for 6 months, respectively, compared to 14.3% in the placebo group, using the crude rates in which subjects who prematurely discontinued without evidence of recurrence are considered to have recurred. When the supportive life-table methods were used which account for the subjects who prematurely discontinued by censoring, the rates were (b) (4) and (b) (4) for the dexlansoprazole MR 60-mg and 90-mg treatment groups compared to 25.7% for the placebo group.

Medical Officer Comments:

The efficacy of both dex doses over placebo is again clearly demonstrated in the above table. There is no difference seen, however, between the 60 mg and 90 mg dex doses.

The table below shows the integrated analysis of both studies for the primary endpoint. Since only the 60 mg dose was studied in both trials, the 30 mg and 90 mg dose results are identical to those presented in the prior two tables.

Table 32: Integrated Analysis for Primary Endpoint for MHEE Studies

Visit	Placebo % (95% CI)	Dexlansoprazole MR			P-value					
		30 mg QD % (95% CI)	60 mg QD % (95% CI)	90 mg QD % (95% CI)	30 mg QD vs placebo	60 mg QD vs placebo	90 mg QD vs placebo	30 mg QD vs 60 mg QD	60 mg QD vs 90 mg QD	
Integrated Analysis										
Primary Crude Rates: ITT Primary Subjects										
	(N=231)	(b) (4)								
Month 1 ^{a,b}	36.8 (30.6, 43.4)	(b) (4)								
Month 3 ^{a,b}	19.5 (14.6, 25.2)	(b) (4)								
Month 6 ^{a,b,c}	14.3 (10.0, 19.5)	(b) (4)								
Supportive Life-Table Rates^d: ITT Subjects										
	(N=235)	(N=137)								
Month 1	44.0 (37.9, 50.0)	89.3 (84.0, 94.6)								
Month 3	30.7 (24.6, 36.9)	80.2 (73.2, 87.2)								
Month 6 ^e	26.4 (20.1, 32.6)	74.9 (67.1, 82.6)								

Source: Table 2.7.3.3.r., p.56, Module 2.7.3, NDA 22-287

Results of the integrated analysis supported the individual study results. The percentage of subjects who maintained healed EE over 6 months was greater in each dexlansoprazole MR treatment group than in the placebo treatment group by both the crude rate analysis and the time-to-event analysis. The difference between the dexlansoprazole MR 60-mg QD and placebo treatment groups was statistically significant by each method of analysis, as it was in each of the individual studies.

Medical Officer Comments:

The integrated analysis for the primary endpoint provides strong supportive evidence of efficacy for the 60 mg dose of dexlansoprazole over placebo.

Taking all of the above information regarding the primary endpoint into account, the reviewer believes that (b) (4)

Although the 30 mg and 90 mg doses were only evaluated in one study, the extremely low p-values seen make it very unlikely that a second confirmatory study would refute the results.

Despite the strong efficacy seen for each dose when compared to placebo, no significant differences between 60 mg and 30 mg or between 90 mg and 60 mg were seen.

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6.2.5 Analysis of Secondary Endpoints

The reviewer will focus only on the key secondary endpoints as prospectively defined by the sponsor. The first key secondary endpoint was:

- Percentage of 24-hour heartburn-free days during treatment (neither daytime nor nighttime heartburn)

The following table demonstrates the results for both individual studies for this secondary endpoint.

Table 33: Percentage of days without heartburn for MHEE studies

Measurement	Placebo	Dexlansoprazole MR		
		30 mg QD	60 mg QD	90 mg QD
Study T-EE05-135	(N=141)	(N=132)	(N=147)	NA
Percentage of 24-hour Heartburn-Free Days				
Q1	5.9	80.7	(b) (4)	
Median	28.6	96.1		
Q3	61.8	100.0		
Mean (SD)	36.0 (32.0)	83.3 (26.6)		
p-value: Dexlansoprazole MR vs Placebo		<0.00001*		
p-value: Dexlansoprazole MR 30 mg QD vs 60 mg QD				
Study T-EE04-086	(N=133)	NA		
Percentage of 24-hour Heartburn-Free Days				
Q1	5.0	NA		
Median	19.2	NA		
Q3	52.0	NA		
Mean (SD)	29.5 (29.3)	NA		
p-value: Dexlansoprazole MR vs Placebo		NA		
p-value: Dexlansoprazole MR 60 mg QD vs 90 mg QD				

Source: Table 2.7.3.3.x., p.76, Module 2.7.3, NDA 22-287

In each study, the percentage of 24-hour heartburn-free days during treatment (neither daytime nor nighttime heartburn as recorded in their daily diary) was statistically significantly higher in subjects in each of the dexlansoprazole MR treatment groups (median range: (b) (4) to 96.1%) compared to the placebo treatment group (medians in Studies T-EE05-135 and T-EE04-086: 28.6% and 19.2%, respectively).

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(b) (4) (dexlansoprazole)

These results were confirmed by the integrated analysis for the 60 mg dose, as shown in the table below.

Table 34: Integrated Analysis for Percentage of days without heartburn for MHEE Studies

Measurement	Placebo	Dexlansoprazole MR		
		30 mg QD	60 mg QD	90 mg QD
Integrated Analysis	(N=274) [†]	(N=132)	(N=304) [†]	(N=147)
Percentage of 24-hour Heartburn-Free Days				
Q1	5.9	80.7	(b) (4)	
Median	22.2	96.1		
Q3	57.1	100.0		
Mean (SD)	32.9 (30.8)	83.3 (26.6)		
p-value: Dexlansoprazole MR 60-mg QD vs Placebo				

Source: Table 2.7.3.3.x., p.77, Module 2.7.3, NDA 22-287

Medical Officer Comments:

The individual study results and the integrated analysis demonstrate clear evidence of efficacy for all dex doses when compared to placebo for this key secondary endpoint. The reviewer also believes that this difference is clinically meaningful.

(b) (4)

The reviewer will defer to the Statistical reviewers for this determination.

No significant differences were seen for this endpoint when comparing dex doses against one another.

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Clinical Review
 Keith B. St. Amand, MD
 NDA 22-287
 (b) (4) (dexlansoprazole)

The second key secondary endpoint was:

- Percentage of days without nighttime heartburn

The following table presents the results for this secondary endpoint for each individual study.

Table 35: Percentage of days without nighttime heartburn for MHEE Studies

Measurement	Placebo	Dexlansoprazole MR		
		30 mg QD	60 mg QD	90 mg QD
Study T-EE05-135	(N=141)	(N=132)	(N=147)	NA
Percentage of Days Without Nighttime Heartburn				
Q1	19.0	89.9	(b) (4)	
Median	71.4	98.8		
Q3	92.3	100.0		
Mean (SD)	57.1 (36.8)	88.7 (22.6)		
p-value: Dexlansoprazole MR vs Placebo		<0.0001*		
p-value: Dexlansoprazole MR 30 mg QD vs 60 mg QD				
Study T-EE04-086	(N=133)	NA		
Percentage of Days Without Nighttime Heartburn				
Q1	14.8	NA		
Median	50.0	NA		
Q3	81.3	NA		
Mean (SD)	48.3 (35.3)	NA		
p-value: Dexlansoprazole MR vs Placebo		NA		
p-value: Dexlansoprazole MR 60 mg QD vs 90 mg QD				

Source: Table 2.7.3.3.x., p.76, Module 2.7.3, NDA 22-287

In each study, the percentage of days without nighttime heartburn during treatment were statistically significantly higher in subjects in each of the dexlansoprazole MR treatment groups (median range: (b) (4) to 98.8%) compared to the placebo treatment group (medians in Studies T-EE05-135 and T-EE04-086: 71.4% and 50.0%, respectively).

These results were confirmed by the integrated analysis for the 60 mg dose, as shown in the table below.

Table 36: Integrated Analysis for Percentage of days without nighttime heartburn for MHEE Studies

Measurement	Placebo	Dexlansoprazole MR		
		30 mg QD	60 mg QD	90 mg QD
Percentage of Days Without Nighttime Heartburn				
Q1	15.4	89.9	(b) (4)	
Median	58.8	98.8		
Q3	89.1	100.0		
Mean (SD)	52.8 (36.3)	88.7 (22.6)		
p-value: Dexlansoprazole MR 60-mg QD vs Placebo				

Source: Table 2.7.3.3.x., p.77, Module 2.7.3, NDA 22-287

Medical Officer Comments:

The individual study results and the integrated analysis demonstrate clear evidence of efficacy for all dex doses when compared to placebo for this key secondary endpoint. The reviewer also believes that this difference is clinically meaningful.

(b) (4)

The reviewer will defer to the Statistical reviewers for this determination.

No significant differences were seen for this endpoint when comparing dex doses against one another.

6.2.6 Subpopulations

The sponsor performed comparisons of the dex doses with placebo for the primary endpoint for the following key subgroups:

- Baseline LA Grade: A or B/ C or D
- Duration of treatment in HEE Study: 4 weeks/ 8 weeks
- Treatment in HEE Study: Dex 60 mg/ Dex 90 or 30 mg (depends on study)/ Lansoprazole 30 mg

The results of these subgroup analyses for Study -135 are shown below.

Table 37: Key Subgroup Analyses for Study -135

	Placebo	Dexlansoprazole MR		p-value		
		30 mg QD	60 mg QD	Dex MR 30 mg QD vs placebo	Dex MR 60 mg QD vs placebo	Dex MR 30 mg QD vs Dex MR 60 mg QD
Subgroup Analyses of Primary Endpoint at Month 6*						
By Grouped Baseline LA Grade (b) (4)						
Primary Crude Rates: [†] ITT Primary						
	N [#]	% (95% CI)	N [#]	N [#]	% (95% CI)	<=0.00001 [†] (b) (4)
A or B	92	16.3 (9.4, 25.5)	86	103	66.0 (56.0, 75.1)	<=0.00001 [†]
C or D	27	7.4 (0.9, 24.3)	39	40	67.5 (50.9, 81.4)	<=0.00001 [†]
By Duration of Treatment in Healing of EE Study						
Primary Crude Rates: [†] ITT Primary Subjects (b) (4)						
	N [#]	% (95% CI)	N [#]	N [#]	% (95% CI)	<=0.00001 [†]
4 weeks	92	15.2 (8.6, 24.2)	93	108	63.9 (54.1, 73.9)	<=0.00001 [†]
8 weeks	26	11.5 (2.4, 30.2)	32	35	74.3 (56.7, 87.5)	<=0.00001 [†]
By Treatment in Healing of EE Study						
Primary Crude Rates: [†] ITT Primary						
	N [#]	% (95% CI)	N [#]	N [#]	% (95% CI)	<=0.00001 [†]
Dex MR 60 mg QD	35	8.6 (1.8, 23.1)	49	45	68.9 (53.4, 81.8)	<=0.00001 [†]
Dex MR 90 mg QD	50	14.0 (5.8, 26.7)	41	49	73.5 (58.9, 85.1)	<=0.00001 [†]
Lan 30 mg QD	34	20.6 (8.7, 37.9)	35	49	57.1 (42.2, 71.2)	0.00159 [†]

Source: Table 2.7.3.2.c., p. 3 [redacted] 7.3, NDA 22-287

(b) (4) dexlansoprazole

The results for the same subgroup analyses for Study -086 are shown below.

Table 38: Key Subgroup Analyses for Study -086

	Dexlansoprazole MR				P-value	
	Placebo	60 mg QD	90 mg QD	Dex MR 60 mg QD vs placebo	Dex MR 90 mg QD vs placebo	Dex MR 60 mg QD vs Dex MR 90 mg QD
Subgroup Analyses of Primary Endpoint at Month 6*						
By Grouped Baseline LA Grade						
Primary Crude Rates:† IIT Primary Subjects						
	N ^c	% (95% CI)	N ^c	% (95% CI)		
A or B	88	17.0 (9.9, 26.6)	117	67.5 (58.2, 75.9)	<0.00001†	(b) (4)
C or D	24	4.2 (0.1, 21.1)	35	62.9 (44.9, 78.5)	<0.00001†	
By Duration of Treatment in EE Healing Study						
Primary Crude Rates:† IIT Primary Subjects						
	N ^c	% (95% CI)	N ^c	% (95% CI)		
4 weeks	103	13.6 (7.6, 21.8)	138	70.3 (61.9, 77.8)	<0.00001†	
8 weeks	9	22.2 (2.8, 60.0)	14	28.6 (6.4, 58.1)	>0.99999	
By Treatment in Healing of EE Study						
Primary Crude Rates:† IIT Primary Subjects						
	N ^c	% (95% CI)	N ^c	% (95% CI)		
Dex MR 60 mg QD	35	14.3 (4.8, 30.3)	49	71.4 (56.7, 83.4)	<0.00001†	
Dex MR 90 mg QD	38	18.4 (7.7, 34.3)	51	72.5 (58.3, 84.1)	<0.00001†	
Lan 30 mg QD	39	10.3 (2.9, 24.2)	52	55.8 (41.5, 69.5)	0.00001†	

Source: Table 2.7.3.2.e., p.34, Module 2.7.3, NDA 22-287

In each study, by the crude rate analysis, the 6-month rates of maintenance of healed EE for the dexlansoprazole MR treatment groups were statistically significantly superior to placebo when adjusted for grouped baseline LA Grade. No statistically significant differences were observed between dexlansoprazole MR dose groups in either study. In each study, the crude percentages of subjects who maintained healed EE at Month 6 were similar across dexlansoprazole MR treatment groups for those subjects with baseline LA Grades A or B. However, for subjects with more severe grades of EE (Grades C or D) at baseline, the therapeutic gain over placebo using the crude rates ranged from 58.7 to (b) (4) percentage points for dexlansoprazole MR 60 mg QD and 90 mg QD in the 2 studies, and was 43.9 percentage points for dexlansoprazole MR 30 mg QD.

Medical Officer Comments:

These findings confirm the superiority of dex for all doses when compared to placebo for the primary endpoint, regardless of subgroup.

6.2.6.1 Comparison of dex doses for key subgroups

- Baseline LA Grade

Among subjects with more severe grades of EE, the therapeutic advantage for the crude maintenance rates of dexlansoprazole MR 60 mg QD over 30 mg QD in Study T-EE05-135 was

(b) (4) (dexlansoprazole)

16.2 percentage points at Month 6. However, the therapeutic advantage of dexlansoprazole MR 60 mg QD over 30 mg QD did not reach statistical significance, which may be due to the small number of subjects with baseline LA Grades C or D.

Likewise, no therapeutic advantage of dexlansoprazole MR 90 mg QD compared to dexlansoprazole MR 60 mg QD was observed in Study T-EE04-086.

- Duration of Treatment in HEE Study

In Study T-EE05-135, dexlansoprazole MR 30-mg QD and 60-mg QD treatment groups demonstrated 6-month crude maintenance rates for subjects healed in 4 weeks of (b) (4) and 63.9%, respectively. The dexlansoprazole MR 60-mg dose had a much higher maintenance of healed EE rate than the dexlansoprazole MR 30-mg dose for subjects who took 8 weeks to heal (74.3% vs. (b) (4)). This difference in the crude maintenance rates between the 2 dexlansoprazole MR doses did not reach statistical significance using a significance level of 0.0025; this may be due to the small number of subjects enrolled in the maintenance study who took 8 weeks to heal in the healing of EE study.

Likewise, in Study -086, similar maintenance rates by crude rate analysis were observed for the dexlansoprazole MR 60-mg QD and 90-mg QD doses for subjects healed in 4 weeks (crude rates of 70.3% and (b) (4) respectively). However, the dexlansoprazole MR 90-mg dose had a higher maintenance of healed EE rate (crude rate difference of (b) (4) percentage points) than the dexlansoprazole MR 60-mg dose for the few subjects enrolled in this study who took 8 weeks to heal. No statistically significant differences between these dexlansoprazole MR doses were observed by either method of analysis.

- Treatment in HEE Study

Both studies showed consistent superiority of dex over placebo regardless of the treatment used during the HEE studies. There were no statistically significant differences seen between dex doses in any of these subgroups.

6.2.6.2 Other Subgroup Analyses

Subgroup analyses for the primary endpoint were also conducted for age, race, gender, BMI, smoking status, alcohol use, caffeine use, H. pylori status, overall study drug compliance, GERD symptom investigator assessment of heartburn, and rescue medication usage.

All subgroups showed consistent statistical superiority of dex over placebo.

(b) (4) (dexlansoprazole)

Medical Officer Comments:

Overall, the subgroup analysis for this primary endpoint:

- 1. confirms the results seen in the ITT population (significant differences seen between treatment groups and comparator for all subgroups);**
- 2. does not reveal any imbalance to indicate that any one subgroup is driving the efficacy results (treatment response rates are similar between male and female, smoker and non-smoker, etc.); and,**
- 3. confirms that there is no evidence that any one dex dose is superior to another dex dose.**

6.2.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The dexlansoprazole MR doses evaluated in Studies T-EE05-135 and T-EE04-086 were chosen, in part, based on results from 2 Phase 1 PK/PD studies. In order to evaluate the relationship between plasma exposure of dexlansoprazole and the pharmacological response, the mean 24-hour intragastric pH, the percentage of time pH was >4, and AUC values for dexlansoprazole following oral administration of dexlansoprazole MR 30 mg, 60 mg, 90 mg, and 120 mg from the Phase 1 PK/PD studies were combined.

Estimates from exposure-response analyses indicated that dexlansoprazole MR doses ranging from 30 mg to 90 mg would result in increasing percentages of time the intragastric pH was >4, while doses higher than 90 mg would be unlikely to provide meaningful additional pharmacological benefit. The analyses supported the inclusion of a 30-mg dose in the development plan for the maintenance of healed EE indication. In addition, selection of doses for the maintenance of healed EE studies was based on analysis of studies and approved doses for the lansoprazole clinical program.

Several lansoprazole studies demonstrated that a lower dose than that required for EE healing was as effective as the higher dose for the treatment of both maintenance of healed EE and symptomatic GERD. Similarly, as doses of dexlansoprazole MR 60 mg and 90 mg were chosen for the healing of EE studies (T-EE04-084 and T-EE04-085), the 30-mg dose of dexlansoprazole MR was selected as a lower dose for evaluation, along with the 60-mg and 90-mg dexlansoprazole MR doses, for both the maintenance of healed EE and symptomatic GERD studies.

Medical Officer Comments:

The approach outlined above is rational from a biopharmaceutical perspective, and the clinical efficacy results as discussed above appear to support the choice of dose in that they demonstrated superiority when compared to placebo.

Although the reviewer agrees that both the 30 mg and 60 mg dose showed efficacy in the MHEE studies, the reviewer does not agree with the sponsor's recommendation that the ^(b)
₍₄₎

(b) (4) (dexlansoprazole)

(b) (4) Although numerical differences were seen in certain subgroups for the 60 mg dex dose when compared to the 30 mg dose, no statistically significant differences were seen, and only one study is available for analyzing this difference. (b) (4)

6.2.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Evaluation of the persistence of efficacy, i.e., the maintenance of healed EE, was the primary objective of the Phase 3 maintenance of healed EE studies, which enrolled subjects who had complete healing in the Phase 3 healing of EE studies. Although subjects were re-randomized before receiving study drug in the maintenance of healed EE studies, all subjects received active PPI treatment (dexlansoprazole MR 60 mg QD or 90 mg QD or lansoprazole 30 mg QD) in the healing of EE studies. Overall, the Phase 3 maintenance of healed EE studies demonstrated that all dexlansoprazole MR doses maintained healing of EE for 6 months for $\geq 64\%$ of subjects by the crude rate analysis or $\geq 75\%$ of subjects by the life-table rates. In contrast, all but 14% of subjects by the crude rates and 26% of subjects by the life-table rates, who received placebo in the maintenance of healed EE studies relapsed within 6 months, and most relapsed by Month 1.

The percentage of subjects who maintained healed EE was very high at Month 1 and similar in the dexlansoprazole MR 30-mg QD, 60-mg QD, and 90-mg QD treatment groups (by crude rates in the integrated analysis: 88.8%, (b) (4) respectively). The rates were still similar across the 3 dexlansoprazole MR treatment groups at Month 3 (74.4%, (b) (4) respectively) and Month 6 (66.4%, (b) (4) respectively). This trend is consistent with maintenance rates observed with other PPIs.

The percentage of subjects in the maintenance of healed EE studies who prematurely discontinued due to therapeutic failure was low. A reason of therapeutic failure was specified at the site's discretion under the "Other" category. Seventeen of 287 (6%) placebo subjects, 0 of 140 dexlansoprazole MR 30-mg QD subjects, 4 of 317 (1%) dexlansoprazole MR 60-mg QD subjects, and 3 of 152 (2%) dexlansoprazole MR 90-mg QD subjects prematurely discontinued with therapeutic failure listed as a reason under the "Other" category.

Medical Officer Comments:

The high percentage of subjects who maintained healed EE at Months 1, 3, and 6 confirms the persistence of treatment effect for dexlansoprazole. It is interesting that slightly more patients on the higher doses (60 and 90 mg) discontinued due to treatment failure, but the reviewer does not believe this difference is clinically meaningful.

6.2.9 Additional Efficacy Issues/Analyses

Medical Officer Comments:

The sponsor's proposed indication for the maintenance of healed EE includes the following language: "maintaining healing of erosive esophagitis (b) (4)" While the

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(b) (4) (dexlansoprazole)

sponsor performed a hierarchical analysis of two key secondary endpoints which address the maintenance of heartburn-free periods, (b) (4)

With this in mind, the reviewer does not believe the sponsor showed sufficient evidence to warrant the language (b) (4)

If the statistical soundness of the key secondary endpoint analysis is confirmed by the Biostatistics reviewers, then language such as “maintaining healing of erosive esophagitis (b) (4) could be included in the label.

6.3 Treatment of GERD

The final indication sought by the sponsor is “treating (b) (4) heartburn (b) (4) associated with GERD.” The sponsor evaluated three dosages for this indication (30 mg daily, 60 mg daily, and 90 mg daily), but is only seeking approval for the 30 mg dose.

6.3.1 Methods

6.3.1.1 Overview of Study Design

Studies T-GD05-137 and T-GD04-082 were both Phase 3, randomized, double-blind, multicenter, placebo-controlled, 3-arm studies with 4-week Treatment Periods. The studies were designed to evaluate symptom relief in subjects with symptomatic, endoscopically confirmed nonerosive GERD over a 4-week Treatment Period, and compare the efficacy of 2 dose levels of dexlansoprazole MR with that of placebo when administered orally as a single daily dose in the morning, before breakfast. In each study, subjects were randomly assigned in a 1:1:1 ratio to receive placebo or 1 of the 2 dexlansoprazole MR doses.

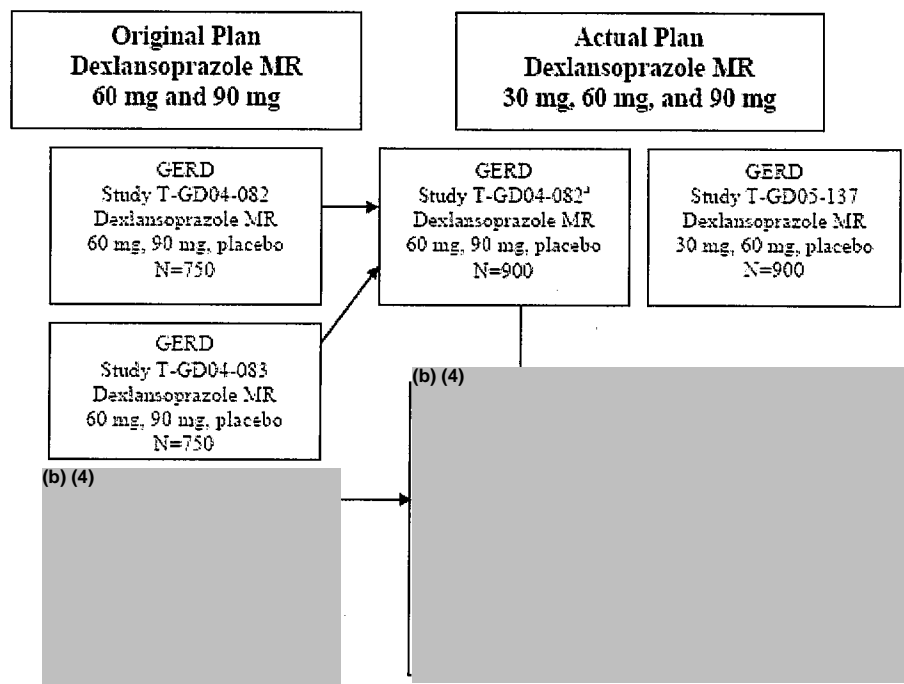
It was previously determined that a 4-week duration of therapy with a PPI is an adequate treatment duration to evaluate efficacy in patients with symptomatic GERD. Placebo is a standard comparator used to evaluate efficacy and safety in subjects with symptomatic GERD.

Medical Officer Comments:

The reviewer concurs with the 4-week duration of therapy and with the choice of comparator for the trials. Non-erosive GERD is not a condition which poses an imminent threat to a patient’s health, so the use of placebo for up to 4 weeks is ethically acceptable.

The following figure shows the development plan for the two randomized controlled studies for GERD as well as the long-term safety study which enrolled patients from Study -082.

Figure 5: Dexlansoprazole MR Symptomatic GERD Clinical Program



Source: Figure 2.7.3.a., p.8, Module 2.7.3, NDA 22-287

It can be seen from the above figure that the dexlansoprazole MR clinical program originally consisted of 2 Phase 3, randomized, controlled study protocols (T-GD04-082 and T-GD04-083) designed to assess the safety and efficacy of dexlansoprazole MR 60 mg and 90 mg in treating symptomatic GERD. Based on PK/PD data from Phase 1 studies, a 30-mg dose was added to the development plan for the symptomatic GERD indication. As the doses of dexlansoprazole MR 60 mg and 90 mg were chosen for the healing of EE studies (T-EE04-084 and T-EE04-085), the 30-mg dose of dexlansoprazole MR was selected as a lower dose for evaluation, along with the 60 mg and 90 mg dexlansoprazole MR doses. This resulted in an additional Phase 3, randomized, controlled study (T-GD05-137) that compared dexlansoprazole MR 30 mg and 60 mg QD vs. placebo. Studies T-GD04-082 and T-GD04-083 were combined into a single large study, hereinafter referred to as Study T-GD04-082.

In addition to conducting the controlled efficacy studies for the symptomatic GERD indication, a Phase 3, open-label, multicenter, long-term safety study of dexlansoprazole MR (60 mg QD and 90 mg QD) was conducted. This 12-month study (Study T-GI04-088) evaluated the safety and long-term quality-of-life (QOL) and symptom severity in subjects with nonerosive GERD. Prior to Amendment 4, subjects who completed the symptomatic GERD Study T-GD04-082 were eligible for enrollment into the long-term study, and were randomly assigned in a 1:1 ratio to receive either dexlansoprazole MR 60 mg QD or dexlansoprazole MR 90 mg QD for 12 months.

The studies consisted of 2 periods: a Screening Period, which lasted a minimum of 7 days and a maximum of 21 days, and a 4-week Treatment Period. Subjects were given rescue medication and an electronic diary on the first day of the Screening Period. Each day of the Screening Period, subjects recorded whether they used rescue medication and documented the presence and maximum severity of daytime and nighttime heartburn symptoms in their electronic diary. In addition, subjects were evaluated by investigator assessment for heartburn, acid regurgitation, dysphagia, belching, and epigastric pain and completed QOL and symptom severity questionnaires. Subjects were instructed not to make any lifestyle changes or alter their usual behaviors to treat their symptoms of GERD throughout the study. Screening evaluations included endoscopy and *H. pylori* testing. Endoscopy data were collected to exclude subjects with EE. Other screening evaluations included medical and social history, physical examination, vital signs, clinical laboratory tests, serum gastrin measurement, and pregnancy test (all females).

During the 4-week Treatment Period, subjects self-administered study drug orally, once a day, before breakfast, and could continue to take rescue medication (open-label Gelusil) as needed (up to 6 tablets in a 24-hour period). Subjects documented the presence and maximum severity of daytime and nighttime heartburn symptoms and recorded usage of rescue medication using the daily electronic diary. Subject visits were conducted at Weeks 2 and 4 of the Treatment Period to collect study drug (Week 4 only) and rescue medication, dispense rescue medication (Week 2 only), assess GERD symptoms, complete QOL and symptom severity questionnaires, review concomitant medication use, and assess adverse events.

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6.3.1.2 Eligibility Criteria

The following table displays the inclusion and exclusion criteria for both sGERD studies.

Table 40: Eligibility criteria for Studies T-GD05-137 and T-GD04-082

Inclusion Criteria	Exclusion Criteria
1. Prior to any study-specific procedures being performed, the subject voluntarily signed an informed consent form (ICF) and any privacy statement/authorization form required by the region in which the subject participated, after having its contents fully explained and all questions answered. An Institutional Review Board approved the ICFs. 2. Male or female subjects at least 18 years of age (and of legal age of consent). 3. All female subjects had a negative serum pregnancy test at screening and a negative urine pregnancy test at Day -1 and were using, and agreed to continued use of, a double barrier method of birth control. Oral, injectable, or patch contraceptives were considered as 1 method if the subject took them for greater than 3 months duration at the Screening Visit. Subjects who had a bilateral tubal ligation or hysterectomy or who were postmenopausal (the absence of menses for 1-2 years with a follicle-stimulating hormone level ≥ 40 IU/L or absence of menses for ≥ 2 years) were not required to use birth control. 4. Subjects identified their main symptom as a burning feeling in the mid-epigastric area and/or chest area (i.e. heartburn). 5. Subject had a history of episodes of heartburn for 6 months or longer prior to screening. 6. Subject was required to have a history of episodes of heartburn for 4 or more days during the 7 days prior to Day -1 as recorded in the electronic diary.	1. Use of prescription or nonprescription PPIs during screening and throughout the study. 2. Use of prescription or nonprescription H₂RA or sucralfate during screening and throughout the study. 3. Chronic use (>12 doses/month) of nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 NSAIDs within 30 days prior to the Screening Period and throughout the study; however, low-dose aspirin up to 325 mg per day was allowed. 4. Use of antacids (except for study supplied Gelnisil [US sites], or a similar equivalent antacid [an-US sites]) during the Screening and Treatment Periods. 5. Subjects who used drugs with significant anticholinergic effects such as tricyclics who could not stay on a stable dose for 4 weeks prior to dosing and throughout the study. 6. Subjects who could not discontinue the use of the following medications prior to the first dose of study drug and throughout the study: misoprostol, prokinetics. 7. Need for continuous anticoagulant therapy. 8. Use of any investigational drug(s) within 30 days of screening. 9. Cancer (except basal cell carcinoma of the skin) within 3 years prior to screening. 10. Any condition that may have required inpatient surgery during the course of the study. 11. Endoscopic Barrett's esophagus and/or definite dysplastic changes in the esophagus. If any suspicious Barrett's esophagus was seen during screening and the principal investigator was confident that the subject would be confirmed with Barrett's, the subject may have been automatically excluded. Otherwise, any suspicious Barrett's esophagus seen during screening endoscopy was biopsied and sent to a local pathology laboratory. Subjects may have been randomized; however, the subject was discontinued if the screening biopsy was found to confirm Barrett's and/or to have definite dysplastic changes. Subjects with indeterminate dysplasia due to severe inflammation may have been enrolled and a repeat endoscopy with biopsy was to be performed at the next visit. 12. Subjects with active gastric or duodenal ulcers within 4 weeks of the first dose of study drug. 13. Subjects with a history of dilatation of esophageal strictures, other than a Schatzki's ring (a ring of mucosal tissue near the lower esophageal sphincter). 14. Subjects with EE, as shown by endoscopy, during the Screening Period. 15. Coexisting diseases affecting the esophagus, (eg, esophageal varices, scleroderma, viral, fungal infection or esophageal stricture), history of radiation therapy or cryotherapy to the esophagus, caustic or physiochemical trauma such as sclerotherapy to the esophagus. 16. Evidence of uncontrolled systemic disease. 17. Subject had abnormal laboratory values that suggested a clinically significant underlying disease or condition that may have prevented the subject from entering the study; or subject with the following lab abnormalities: creatinine ≥ 1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $>2.5X$ the upper limit of normal, or bilirubin ≥ 2.0 mg/dL with AST:ALT elevated above normal values. 18. Subject known to have acquired immunodeficiency syndrome. 19. Current or historical evidence of Zollinger-Ellison syndrome or other hypersecretory condition. 20. History of gastric, duodenal, or esophageal surgery, except simple oversew of an ulcer. 21. Acute upper gastrointestinal hemorrhage within 4 weeks of endoscopy. 22. Subject received blood products within 3 months prior to the first dose of study drug. 23. Known hypersensitivity to any PPI (including lansoprazole, omeprazole, rabeprazole, pantoprazole or esomeprazole), any component of dexlansoprazole MR, or Gelnisil/antacid. 24. Females who were pregnant or lactating. 25. History of alcohol abuse [≥ 21 units (1 unit=12 ounce (oz) beer, 1.5 oz hard liquor, or 5 oz wine) per week] or illegal drug use or drug addiction in the 12 months prior to screening. 26. Subject had participated in a previous dexlansoprazole MR study. 27. Subjects who, in the opinion of the investigator, were unable to comply with the requirements of the study or were unsuitable for any reason.

Source: Table 2.7.3.d., p.26, Module 2.7.3, NDA 22-287

Medical Officer Comments:

The eligibility criteria as listed above are acceptable.

6.3.1.3 Efficacy Endpoints

An overview of the endpoints for the two studies is presented below:

Primary Efficacy Variable

- Percentage of days with neither daytime nor nighttime heartburn during treatment, as assessed by daily diary.

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Medical Officer Comments:

The primary endpoint is fairly self-explanatory and appears to provide information to support the efficacy of dex in treating heartburn **(b) (4)**.

(b) (4)

The reviewer will first examine the efficacy findings at face value to determine their statistical significance; the results of this analysis will be presented in Section 6.3.4 below. The reviewer will then focus on the clinical relevance of the language sought for the indication in Section 6.3.9.

Secondary Efficacy Variable

- Percentage of days without nighttime heartburn during treatment, as assessed by daily diary.

Additional Efficacy Variables

- Percentage of days without daytime heartburn during treatment, as assessed by daily diary.
- Mean severity of daytime and nighttime heartburn during treatment, as assessed by daily diary.
- Mean severity of daytime heartburn during treatment, as assessed by daily diary.
- Mean severity of nighttime heartburn during treatment, as assessed by daily diary.
- Percentage of subjects with neither daytime nor nighttime heartburn over the first 3 days of treatment, as assessed by daily diary.
- Percentage of subjects without daytime heartburn over the first 3 days of treatment, as assessed by daily diary.
- Percentage of subjects without nighttime heartburn over the first 3 days of treatment, as assessed by daily diary.
- Percentage of subjects with sustained resolution of heartburn, defined as 7 consecutive days with neither daytime nor nighttime heartburn, as assessed by daily diary.
- Percentage of days without rescue medication during treatment, as assessed by daily diary.
- Severity of GERD symptoms at Week 2, Week 4, and Final Visit, as assessed by the investigator.
- Change from baseline in PAGO-QOL and PAGO-SYM measurements at Week 2, Week 4, and Final Visit.

Medical Officer Comments:

The sponsor chose a large number of secondary endpoints for study; however, they have designated only one as “secondary,” while the others are considered “additional.” Since a hierarchical testing strategy was employed for the “secondary” endpoint and it could potentially be included in labeling, the reviewer has renamed it as a “key secondary

endpoint.” However, the sponsor-designated “additional endpoints” will not be eligible for inclusion in labeling. Moreover, the reviewer believes that these endpoints provide a relatively insignificant contribution toward demonstrating the efficacy of the product when compared to the primary and key secondary efficacy findings. For these reasons, the reviewer has chosen not to present a written review of these endpoints and will instead focus on presenting a detailed review of the primary and “key secondary” efficacy data.

6.3.1.4 Statistical Considerations

Analyses for the primary and secondary efficacy variables in both controlled symptomatic GERD studies were conducted on separate intent-to-treat (ITT) populations, which included all randomized subjects who received ≥ 1 dose of study drug and completed the appropriate diary entry for the corresponding efficacy variable on ≥ 1 day during treatment. Subjects with confirmed Barrett’s esophagus and/or definite dysplastic changes were to be prematurely discontinued from the study and were excluded from the analyses.

The percentage of days with neither daytime nor nighttime heartburn during treatment and the percentage of days without nighttime heartburn during treatment were summarized by treatment group. Comparisons between the treatment groups were made using Wilcoxon rank-sum tests. The percentage of days with neither daytime nor nighttime heartburn during treatment was also analyzed using a van Elteren test with investigator as the stratification factor. For each efficacy variable, the overall 0.0025 level of significance for the multiple comparisons of each dexlansoprazole MR dose to placebo was controlled within each study using Hochberg’s method.

Regarding the key secondary endpoint, comparisons between dex and placebo will be made with a Wilcoxon rank-sum test for each dex dose that is found to be superior to placebo for the primary efficacy variable. If both dex doses are declared superior to placebo in the primary efficacy analysis, the 0.0025 level of significance for this secondary efficacy variable will be controlled using Hochberg’s method.

Medical Officer Comments:

The sponsor appears to have designed these studies to maintain acceptable Type I error control for the multiple comparisons between different dex doses for the primary and key secondary endpoints. However, final determination of the statistical soundness of the sponsor’s methods will be made by the Biostatistics reviewers for this application. Please see their respective reviews for a more detailed analysis.

6.3.2 Demographics/Baseline Characteristics

The following table presents the integrated demographics and baseline characteristics of the ITT population from both sGERD studies.

Table 41: Demographics & Baseline Characteristics of ITT Subjects, Integrated Analysis of sGERD Studies

Variable	Placebo (N=600)	Dexlansoprazole MR			All ITT Subjects (N=1823)
		30 mg QD (N=312)	60 mg QD (N=613)	90 mg QD (N=298)	
Gender: n (%)					
Male	156 (26.0)	84 (26.9)	196 (32.0)	89 (29.9)	525 (28.8)
Female	444 (74.0)	228 (73.1)	417 (68.0)	209 (70.1)	1298 (71.2)
Ethnicity: n (%)					
Hispanic or Latino	119 (19.8)	66 (21.2)	109 (17.8)	60 (20.1)	354 (19.4)
Not Hispanic or Latino	481 (80.2)	246 (78.8)	504 (82.2)	238 (79.9)	1469 (80.6)
Race: n (%)					
American Indian/Alaskan Native	6 (1.0)	0	5 (0.8)	8 (2.7)	19 (1.0)
Asian	14 (2.3)	4 (1.3)	19 (3.1)	7 (2.3)	44 (2.4)
Black	78 (13.0)	37 (11.9)	91 (14.8)	41 (13.8)	247 (13.5)
Native Hawaiian or Other Pacific Islander	4 (0.7)	1 (0.3)	3 (0.5)	0	8 (0.4)
White	487 (81.2)	265 (84.9)	486 (79.3)	240 (80.5)	1478 (81.1)
Multiracial	9 (1.5)	3 (1.0)	7 (1.1)	2 (0.7)	21 (1.2)
Unknown	2 (0.3)	2 (0.6)	2 (0.3)	0	6 (0.3)
Age (years)					
<45	232 (38.7)	129 (41.3)	258 (42.1)	131 (44.0)	750 (41.1)
45 to <65	291 (48.5)	148 (47.4)	285 (46.5)	137 (46.0)	861 (47.2)
≥65	77 (12.8)	35 (11.2)	70 (11.4)	30 (10.1)	212 (11.6)
Mean (SD)	48.3 (14.00)	47.6 (13.57)	47.7 (13.57)	46.9 (13.70)	47.8 (13.75)
Median	49.0	48.0	47.0	47.0	48.0
Min-Max	19-86	18-78	18-82	18-80	18-86
Weight (kg)					
N	600	312	610	298	1820
Mean (SD)	81.4 (20.18)	80.9 (20.05)	82.2 (19.66)	81.5 (18.32)	81.6 (19.68)
Median	78.5	77.5	79.9	79.1	79.0
Min-Max	41-166	42-165	44-163	48-148	41-168
Height (cm)					
N	599	311	611	294	1815
Mean (SD)	166.1 (9.50)	166.8 (9.45)	166.8 (9.56)	166.3 (9.49)	166.4 (9.51)
Median	165.1	165.1	165.1	165.1	165.1
Min-Max	128-194	133-193	125-199	137-193	125-199
BMI (kg/m²)					
<25	178 (29.7)	89 (28.5)	160 (26.1)	72 (24.2)	499 (27.4)
25 to <30	180 (30.0)	107 (34.3)	207 (33.8)	97 (32.6)	591 (32.4)
≥30	241 (40.2)	115 (36.9)	241 (39.3)	125 (41.9)	722 (39.6)
Missing	1 (0.2)	1 (0.3)	5 (0.8)	4 (1.3)	11 (0.6)
N	599	311	608	294	1812
Mean (SD)	29.5 (6.96)	29.0 (6.75)	29.6 (6.96)	29.5 (6.14)	29.5 (6.80)
Median	28.0	28.0	28.7	28.9	28.4
Min-Max	17-59	17-68	18-71	19-51	17-71

Source: Table 2.7.3.f, p.28, Module 2.7.3, NDA 22-287

In the integrated analyses, the majority of ITT subjects was female (71.2%), the majority was White (81.1%), the majority was not Hispanic or Latino (80.6%), the majority was ≥ 45 years of age (58.8%), and the majority had a BMI ≥ 25 kg/m² (71.8%). No statistically significant differences were observed among treatment groups for any baseline demographic characteristic.

(b) (4) (dexlansoprazole)

Medical Officer Comments:

The above demographics are consistent with those of the patient population likely to require and receive treatment for sGERD.

The following table presents variables that pertain to the social history of enrolled subjects.

Table 42: Social History: Integrated Analysis of sGERD Studies

Variable	Treatment Group n (%)				All ITT Subjects (N=1823)
	Placebo (N=600)	Dexlansoprazole MR			
		30 mg QD (N=312)	60 mg QD (N=613)	90 mg QD (N=298)	
Alcohol Use					
Drinker	324 (54.0)	159 (51.0)	348 (56.8)	167 (56.0)	998 (54.7)
Non-/Ex-drinker	276 (46.0)	153 (49.0)	265 (43.2)	131 (44.0)	825 (45.3)
Smoking Status					
Smoker	103 (17.2)	69 (22.1)	110 (17.9)	64 (21.5)	346 (19.0)
Non-/Ex-smoker	497 (82.8)	243 (77.9)	503 (82.1)	234 (78.5)	1477 (81.0)
Caffeine Use*					
Caffeine User	465 (77.5)	266 (85.3)	486 (79.3)	244 (81.9)	1461 (80.1)
Non-caffeine User	135 (22.5)	46 (14.7)	127 (20.7)	54 (18.1)	362 (19.9)

Source: Table 2.7.3.h., p.31, Module 2.7.3, NDA 22-287

In the integrated analysis, more than half of all ITT subjects used alcohol, the majority of subjects were non-/ex-smokers, and the majority used caffeine. A statistically significant difference was observed among treatment groups for the percentage of ITT subjects that were caffeine users. A slightly higher percentage of ITT subjects in the dexlansoprazole MR 30 mg QD treatment group were caffeine users (85%) compared with the other treatment groups (range 78%-82%).

Medical Officer Comments:

The statistically significant difference seen in caffeine users on the 30 mg dex dose was only present in the integrated analysis. The individual studies did not reveal a statistically significant difference for this covariate. Moreover, the higher use of caffeine would likely have decreased the response rate in the 30 mg group compared to placebo, and thus would have been disadvantageous to the study drug. With this in mind, the reviewer does not believe this slight imbalance compromised the analysis of the product's efficacy for this indication.

The following table shows the *H. pylori* status of enrolled subjects.

Table 43: Baseline *H. pylori* status: Integrated Analysis of sGERD Studies

<i>H. pylori</i> Status*	Placebo (N=600)	30 mg QD (N=312)	60 mg QD (N=613)	90 mg QD (N=298)	All ITT Subjects (N=1823)
Positive	184 (30.7)	94 (30.1)	188 (30.7)	86 (28.9)	552 (30.3)
Negative	416 (69.3)	214 (68.6)	422 (68.8)	212 (71.1)	1264 (69.3)
Unknown	0	4 (1.3)	3 (0.5)	0	7 (0.4)

Source: Table 2.7.3.h., p. 31, Module 2.7.3, NDA 22-287

(b) (4) (dexlansoprazole)

In the integrated analysis, subjects had less nighttime than daytime heartburn at baseline; 41% of all ITT subjects had 6 to 7 days with nighttime heartburn at baseline compared to 63% with 6 to 7 days of daytime heartburn at baseline. Overall, 77% had 6 to 7 days of daytime or nighttime (daytime/nighttime) heartburn at baseline. No statistically significant differences among treatment groups were observed for these baseline variables.

In Study T-GD05-137, subjects had less nighttime than daytime heartburn at baseline; 40% of all ITT subjects had 6 to 7 days with nighttime heartburn at baseline, compared to 60% with 6 to 7 days of daytime heartburn at baseline. Overall, 75% had 6 to 7 days of daytime or nighttime (daytime/nighttime) heartburn at baseline. There was no statistically significant difference among treatment groups in the number of days with baseline daytime or with nighttime heartburn. A statistically significant difference was observed among treatment groups in the number of days with baseline daytime/nighttime heartburn (either daytime or nighttime heartburn or both daytime and nighttime heartburn). In the placebo and dexlansoprazole MR 30-mg QD treatment groups, a slightly higher percentage of subjects had 6 to 7 days of daytime/nighttime heartburn compared to the dexlansoprazole MR 60-mg QD treatment group (80% and 76% vs. 68%, respectively). Conversely, a higher percentage of subjects in the dexlansoprazole MR 60-mg QD treatment group had 4 to 5 days of daytime/nighttime heartburn compared to the placebo and dexlansoprazole MR 30-mg QD treatment groups (30% vs. 17% and 21%, respectively).

In Study T-GD04-082, subjects had less nighttime than daytime heartburn at baseline; 43% of all ITT subjects had 6 to 7 days with nighttime heartburn at baseline, compared to 66% with 6 to 7 days of daytime heartburn at baseline. Overall, 79% had 6 to 7 days of daytime or nighttime (daytime/nighttime) heartburn at baseline. There were no statistically significant differences among treatment groups in baseline number of days that subjects had daytime heartburn or daytime/nighttime heartburn. There was a statistically significant difference among treatment groups in baseline number of days with nighttime heartburn. A slightly higher percentage of placebo subjects had 0 to 3 days of nighttime heartburn compared to the dexlansoprazole MR 60-mg and 90-mg QD treatment groups (38% vs. 29% and 31%, respectively). Conversely, a slightly higher percentage of subjects in the dexlansoprazole MR 60-mg QD and 90-mg QD treatment groups had 6 to 7 days of nighttime heartburn compared to the placebo treatment group (45% and 47% vs. 36%, respectively).

Medical Officer Comments:

The reviewer does not believe that these imbalances are relevant to the analysis of the efficacy of the product since the sponsor is only seeking approval for the 30 mg dose.

In each study, baseline mean severity of daytime heartburn, nighttime heartburn, and daytime/nighttime heartburn was mild to moderate with no statistically significant differences among treatment groups. There were no statistically significant differences among treatment groups in baseline number of days with rescue medication use during the daytime, nighttime, or daytime and nighttime.

(b) (4) (dexlansoprazole)

In each controlled study, there were no statistically significant differences among treatment groups for any GERD symptom, as assessed by investigator at baseline. Of note, at baseline in each study, approximately 85% of ITT subjects had acid regurgitation; 80% had belching; 75% had epigastric pain; and 30% had dysphagia. Approximately half of the subjects' heartburn was moderate in severity (46%-53% across treatment groups in the 2 studies).

In each controlled study, there were no statistically significant differences among treatment groups for the total score or for any subscale of the PAGI-QOL or PAGI-SYM questionnaires at baseline.

Medical Officer Comments:

The overall demographics/ baseline variables for the patients enrolled in the two sGERD studies appear to be well-balanced.

6.3.3 Drug Exposure/Compliance/Patient Disposition

6.3.3.1 Drug Exposure

The following table presents the study drug exposure for both sGERD studies.

Table 44: Study Drug Exposure for ITT Subjects: Integrated Analysis of sGERD Studies

	Placebo (N=600)	Dexlansoprazole MR			All ITT Subjects (N=1823)
		30 mg QD (N=312)	60 mg QD (N=613)	90 mg QD (N=298)	
Total Days on Study Drug					
Mean (SD)	27.5 (5.65)	28.4 (4.87)	28.1 (5.83)	27.6 (5.70)	27.9 (5.60)
Median	28.0	28.0	28.0	28.0	28.0
Minimum-Maximum	1-38	1-44	1-58	1-38	1-58
Cumulative Days on Study Drug, n (%)					
≥1	600 (100)	312 (100)	613 (100)	298 (100)	1823 (100)
≥7	584 (97)	309 (99)	599 (98)	291 (98)	1783 (98)
≥14	571 (95)	304 (97)	589 (96)	285 (96)	1749 (96)
≥21	558 (93)	297 (95)	574 (94)	278 (93)	1707 (94)
≥28	436 (73)	243 (78)	473 (77)	211 (71)	1363 (75)
≥35	20 (3)	21 (7)	42 (7)	17 (6)	100 (5)

Source: Table 2.7.3.c., p.24, Module 2.7.3, NDA 22-287

Symptomatic GERD subjects in both Study T-GD05-137 and Study T-GD04-082 were scheduled to receive dexlansoprazole MR or placebo for 4 weeks. Due to visit scheduling and the dispensing of 35 days of study drug to each subject, the majority of ITT subjects (71% to 78% across the treatment groups) completed ≥28 days of treatment. The median number of days on study drug was the same across all treatment groups (28.0 days). The exposure estimates included any gaps in dosing. Therefore, a small percentage of subjects (3% to 7% across treatment groups) had cumulative exposure ≥35 days.

(b) (4) (dexlansoprazole)

Medical Officer Comments:

Study drug exposure appears to have been similar among the treatment arms.

6.3.3.2 Study Drug Compliance

In the integrated analysis, study drug compliance was similar across all treatment groups for ITT subjects, as exhibited by the mean percent compliance in each treatment group (97.3%-97.8% across treatment groups).

Likewise, diary compliance for all ITT subjects was similar across treatment groups, as exhibited by the mean percentages of expected entries that were completed in each treatment group (83.6%-87.6% across treatment groups).

Medical Officer Comments:

The above rates of study drug compliance should have afforded an adequate evaluation of the drug’s efficacy.

6.3.3.3 Patient Disposition

The following table illustrates the reasons for premature discontinuation from the HEE studies.

**Table 45: Summary of Primary Reasons for Premature Discontinuation:
 Integrated Analysis of sGERD Studies**

Primary Reason for Discontinuation	Treatment Group n (%)				All Subjects (N=1855)
	Placebo (N=609)	Dexlansoprazole MR			
		30 mg QD (N=315)	60 mg QD (N=627)	90 mg QD (N=304)	
Total Subjects Prematurely Discontinued	55 (9)	21 (7)	53 (8)	27 (9)	156 (8)
Adverse Event	16 (3)	6 (2)	17 (3)	11 (4)	50 (3)
Protocol Violation	0	1 (<1)	1 (<1)	0	2 (<1)
Lost to Follow-Up	6 (<1)	4 (1)	4 (<1)	5 (2)	19 (1)
Withdrew Consent	21 (3)	6 (2)	12 (2)	3 (<1)	42 (2)
Did Not Meet Inclusion/Exclusion Criteria	3 (<1)	1 (<1)	11 (2)	5 (2)	20 (1)
Other	9 (1)	3 (<1)	8 (1)	3 (<1)	23 (1)
Lack of efficacy	6	1	3	0	10
Noncompliant	0	0	4	2	6
Pregnancy	0	1	1	0	2
Per subject request	1	0	0	1	2
Per investigator request	2	0	0	0	2
Per Sponsor request (high fasting gastrin level at baseline)	0	1	0	0	1

Source: Table 2.7.3.j., p.36, Module 2.7.3, NDA 22-287

A total of 156 (8%) subjects prematurely discontinued from the GERD studies and the discontinuation rates were similar across the treatment groups. There was no statistically significant difference between dexlansoprazole MR 60 mg QD and placebo (the only treatments tested in both studies) in the percentage of subjects who prematurely discontinued overall or due to any primary reason.

Clinical Review
 Keith B. St. Amand, MD
 NDA 22-287
 (b) (4) (dexlansoprazole)

Medical Officer Comments:

Patient disposition was similar for each treatment arm.

6.3.4 Analysis of Primary Endpoint

As discussed in Section 6.3.1.3 above, the primary endpoint for both sGERD studies was the percentage of days with neither daytime nor nighttime heartburn during treatment, as assessed by daily diary.

The following table shows the results for the primary endpoint for each study as well as for the integrated analysis (applicable only to the 60 mg dose).

Table 46: Percentage of Days With Neither Daytime nor Nighttime Heartburn For sGERD Studies

Percentage of Days With Neither Daytime nor Nighttime Heartburn	Placebo	Dexlansoprazole MR		
		30 mg QD	60 mg QD	90 mg QD
Study T-GD05-137	(N=310)	(N=312)	(b) (4)	
n	310	312		
Median	18.5	54.9		
Mean (SD)	25.0 (25.6)	50.3 (33.9)		
p-value dexlansoprazole MR vs placebo		<0.00001†		
p-value vs dexlansoprazole MR 30 mg				
Study T-GD04-082	(N=290)	NA		
n	290	NA		
Median	17.0	NA		
Mean (SD)	24.9 (25.7)	NA		
p-value dexlansoprazole MR vs placebo		NA		
p-value vs dexlansoprazole MR 60 mg		NA		
Integrated Analysis	(N=600)	(N=312)		
n	600	312		
Median	17.8	54.9		
Mean (SD)	25.0 (25.6)	50.3 (33.9)		
p-value dexlansoprazole MR vs placebo				

Source: Table 2.7.3.1, p.39, Module 2.7.3, NDA 22-287

In each controlled study, the percentage of days that subjects had neither daytime nor nighttime heartburn during treatment according to daily electronic diary was statistically significantly greater in both dexlansoprazole MR treatment groups (30-mg QD and 60-mg QD in Study T-GD05-137, and 60-mg QD and 90-mg QD in Study T-GD04-082) than in the placebo treatment group. No statistically significant difference was observed between the dexlansoprazole MR treatment groups for this endpoint in either study.

The dexlansoprazole MR 60-mg QD dose was the only dexlansoprazole MR dose that was used in both of the Phase 3 symptomatic GERD studies, and the data for this dose were consistent between the 2 studies, as were the placebo results. In addition, the integrated analysis supported the results from the individual studies.

Clinical Review
Keith B. St. Amand, MD
NDA 22-287
(b) (4) (dexlansoprazole)

Medical Officer Comments:

The results presented above show very strong evidence of efficacy for all doses of dex when compared to placebo. The treatment differences are very large (25.3% for the 30 mg dex dose, ^{(b) (4)} for the 60 mg dex dose, and ^{(b) (4)} for the 90 mg dex dose), with very low p-values. Thus, although only one study was performed using the proposed 30 mg dose, the results of a second confirmatory study are extremely unlikely to refute the current findings.

Interestingly, there was no significant difference seen between any two dex doses, and there is no evidence of a dose-response trend. This is consistent with the studies performed in support of the other indications for this NDA as well (see Sections 6.1 and 6.2).

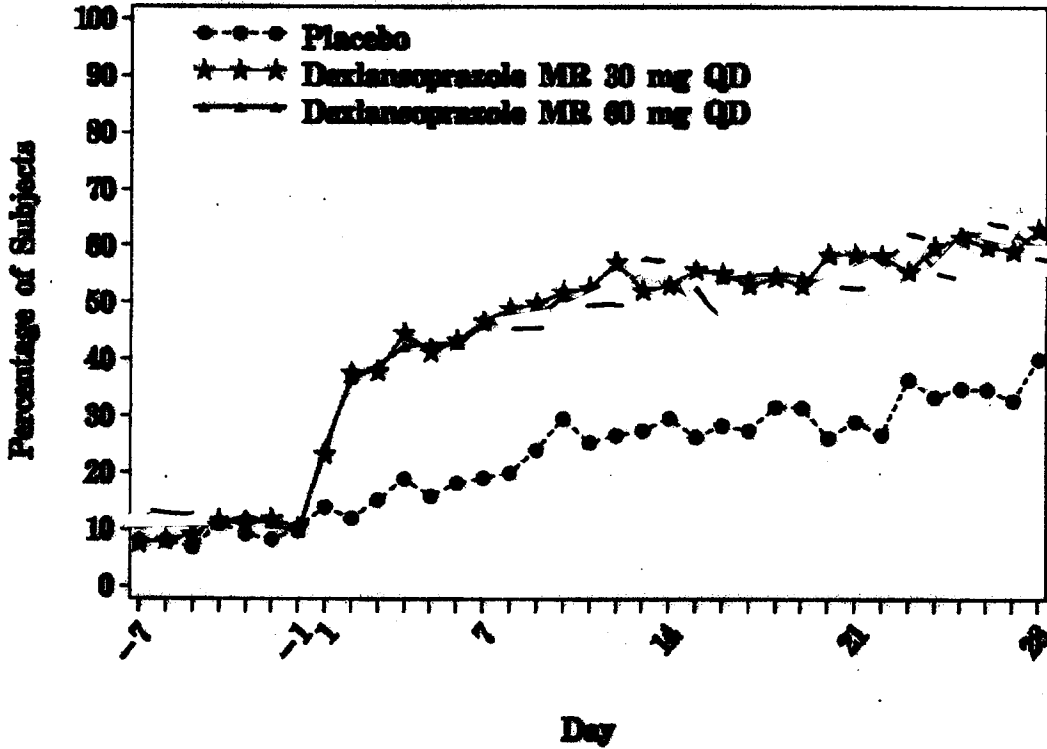
The treatment difference seen with the 30 mg dose of dex translates to approximately 7.1 fewer days with neither daytime nor nighttime heartburn in one month of treatment. The reviewer thus agrees with the sponsor that dex 30 mg provides clinically meaningful benefit to patients when compared to placebo, and that no additional benefit is derived from the higher doses of dex studied for this indication.

The following figures show that a higher percentage of subjects in the dexlansoprazole MR treatment groups had neither daytime nor nighttime heartburn compared to placebo as early as the first 3 days of treatment in each study, and this effect was sustained throughout the Treatment Period.

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Figure 6: Percentage of Subjects with neither daytime nor nighttime heartburn by day:
Study -137

b(4)



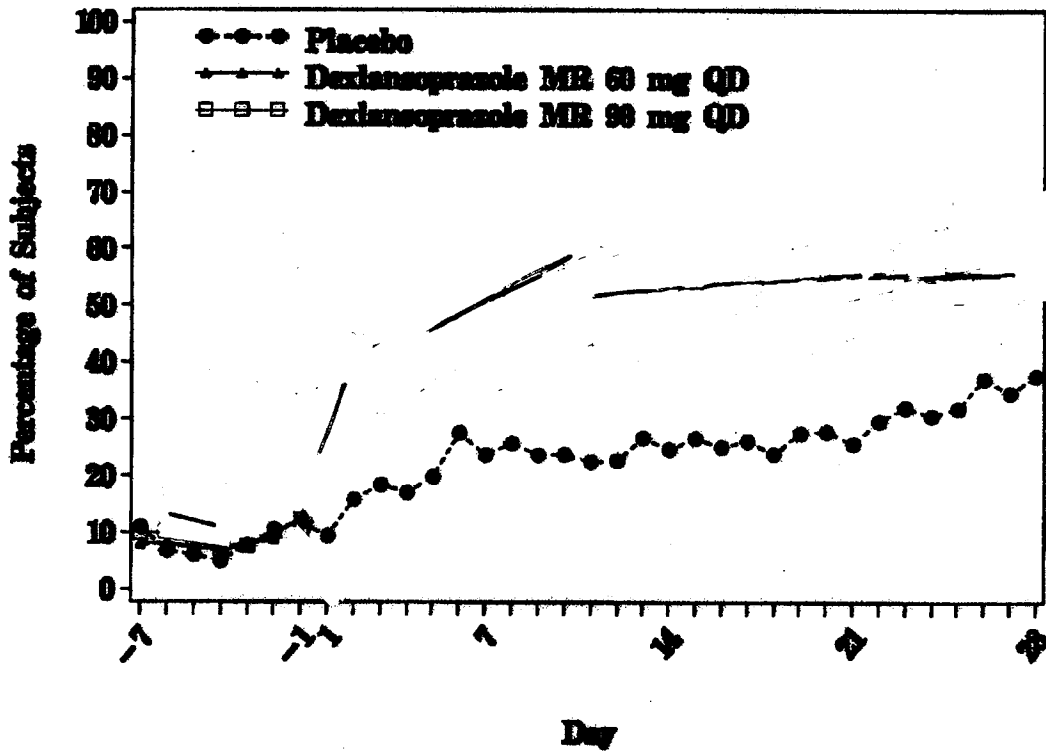
b(4)

Source: Figure 2.7.3.b., p.40, Module 2.7.3, NDA 22-287

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b(4)

**Figure 7: Percentage of Subjects with neither daytime nor nighttime heartburn by day:
Study -082**



b(4)

Source: Figure 2.7.3.c., p.41, Module 2.7.3, NDA 22-287

Medical Officer Comments:

The figures above demonstrate a rapid and sustained treatment effect with dex when compared to placebo. However, neither study revealed any differences between the two dex doses in terms of the onset of symptom relief or duration of relief.

6.3.5 Analysis of Secondary Endpoints

As mentioned above, the reviewer will focus only on the key secondary endpoint of "percentage of days without nighttime heartburn."

The following table shows the results for this endpoint for each study as well as the integrated analysis for the 60 mg dose.

Table 47: Percentage of days without nighttime heartburn for sGERD Studies

Percentage of Days Without Nighttime Heartburn	Placebo	Dexlansoprazole MR	
		30 mg QD	60 mg QD 90 mg QD
Study T-GD05-137	(N=310)	(N=312)	(b) (4)
n	308	311	
Median	51.7	80.8	
Mean (SD)	47.1 (32.6)	67.6 (34.1)	
p-value dexlansoprazole MR vs placebo		<0.00001 [†]	
p-value vs dexlansoprazole MR 30 mg			
Study T-GD04-082	(N=290)	NA	
n	290	NA	
Median	51.0	NA	
Mean (SD)	49.6 (34.1)	NA	
p-value dexlansoprazole MR vs placebo		NA	
p-value vs dexlansoprazole MR 60 mg		NA	
Integrated Analysis	(N=600)	(N=312)	
n	598	311	
Median	51.7	80.8	
Mean (SD)	48.3 (33.3)	67.6 (34.1)	
p-value dexlansoprazole MR vs placebo			

Source: Table 2.7.3.m., p.42, Module 2.7.3, NDA 22-287

In each controlled study, the percentage of days that subjects had no nighttime heartburn during treatment, according to daily electronic diary, was statistically significantly greater in both dexlansoprazole MR treatment groups (30-mg QD and 60-mg QD in Study T-GD05-137, and 60-mg QD and 90-mg QD in Study T-GD04-082) than in the placebo treatment group. No statistically significant difference was observed between the dexlansoprazole MR treatment groups for this endpoint in either study. The dexlansoprazole MR 60-mg QD dose was the only dexlansoprazole MR dose that was used in both of the Phase 3 symptomatic GERD studies, and the data for this dose were consistent between the 2 studies. In addition, the integrated analysis supported the results from the individual studies.

Medical Officer Comments:

The findings for this key secondary endpoint supported the findings of the primary endpoint. Compared to the primary endpoint of heartburn-free days and nights, a higher percentage of heartburn-free nights was reported for patients on placebo (47.1% vs. 25%), but this increase was mirrored in patients on the 30 mg dose of dex (67.6% vs. 50.3%). The overall treatment difference for the secondary endpoint between the 30 mg dose of dex and placebo was thus still quite large (20.5%) and clinically meaningful.

(b) (4)

(b) (4)

As with the primary endpoint, no differences were seen between dex doses for the key secondary endpoint.

6.3.6 Subpopulations

Integrated subgroup analyses of the primary efficacy variable (percentage of days with neither daytime nor nighttime heartburn during treatment) were conducted by combining data from both symptomatic GERD studies. The subgroups included demographic and baseline characteristics (age, gender, race, and BMI category), social history (alcohol use, smoking status, and caffeine use), baseline *H. pylori* status, overall study drug compliance, and the baseline presence and severity of heartburn (number of days with heartburn, mean severity of heartburn, and heartburn severity according to investigator assessment).

The efficacy of dexlansoprazole MR was demonstrated for all 3 doses compared to placebo for each subgroup and the magnitude of heartburn relief was generally similar among the dexlansoprazole MR doses in each subgroup. While some differences in efficacy were noted between some subgroup levels within the dexlansoprazole MR doses, none of the differences were considered to be clinically meaningful. Interpretation within some subgroups was limited due to small sample sizes.

The following table presents the percentage of days with neither daytime nor nighttime heartburn by subgroup for both studies combined.

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Table 48: Percentage of Days With Neither Daytime nor Nighttime Heartburn by Subgroup for sGERD Studies Combined

Percentage of Days With Neither Daytime nor Nighttime Heartburn	Placebo	Dexlansoprazole MR		
		30 mg QD	60 mg QD	90 mg QD
Age (years)				
<45	(N=232)	(N=129)	(b) (4)	
Median	19.1	54.5		
Mean (SD)	25.7 (26.3)	47.8 (33.0)		
45-65	(N=291)	(N=148)		
Median	14.8	53.5		
Mean (SD)	22.9 (24.3)	51.0 (34.6)		
≥65	(N=77)	(N=35)		
Median	29.4	64.3		
Mean (SD)	30.8 (27.7)	57.0 (34.1)		
Gender				
Males	(N=156)	(N=84)		
Median	16.4	55.4		
Mean (SD)	23.3 (25.7)	49.6 (36.3)		
Females	(N=444)	(N=228)		
Median	18.5	54.8		
Mean (SD)	25.6 (25.6)	50.6 (33.1)		
Race				
White	(N=487)	(N=265)		
Median	18.5	57.7		
Mean (SD)	25.0 (25.1)	52.5 (33.1)		
Black	(N=78)	(N=37)		
Median	12.3	40.0		
Mean (SD)	25.0 (27.3)	41.6 (36.6)		
Other	(N=33)	(N=8)		
Median	8.0	13.6		
Mean (SD)	23.2 (29.3)	26.7 (35.8)		
BMI Category (kg/m²)				
<25	(N=178)	(N=89)		
Median	20.7	51.9		
Mean (SD)	26.3 (25.4)	47.8 (32.5)		
25-30	(N=180)	(N=107)		
Median	16.1	57.7		
Mean (SD)	24.5 (25.7)	49.9 (34.4)		
≥30	(N=241)	(N=115)		
Median	15.4	56.0		
Mean (SD)	24.4 (25.8)	52.3 (34.5)		
Baseline <i>H. pylori</i> Status				
Positive	(N=184)	(N=94)		
Median	19.6	51.0		
Mean (SD)	25.9 (25.0)	47.8 (35.7)		
Negative	(N=416)	(N=214)		
Median	15.6	56.1		
Mean (SD)	24.6 (25.9)	51.3 (33.4)		

Source: Tables 2.7.3.r., 2.7.3.s., p.58, 60, Module 2.7.3, NDA 22-287

In addition to the subgroups listed above, analyses were carried out for the following:

- Alcohol drinkers vs. non-/ex-drinkers
- Smokers vs. non-/ex-smokers

(b) (4) dexlansoprazole)

- Caffeine users vs. non-caffeine users
- Baseline number of days of heartburn
- Baseline severity of heartburn
- Investigator assessment of severity of heartburn at baseline

Mild differences in efficacy were seen between subgroups for some of these covariates, but in all cases superiority of dex over placebo was maintained.

Medical Officer Comments:

The subgroup analyses are consistently supportive of the efficacy of dex over placebo for the treatment of heartburn. The minor differences seen in the social history covariates are not clinically meaningful and do not reveal an imbalance that would indicate that any one subgroup is driving the efficacy results.

6.3.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Several lansoprazole studies demonstrated that a lower dose than that required for EE healing was as effective as the healing of EE dose for the treatment of both symptomatic GERD and maintenance of healed EE. Similarly, as the doses of dexlansoprazole MR 60 mg and 90 mg were chosen for the healing of EE studies (T-EE04-084 and T-EE04-085), the 30-mg dose of dexlansoprazole MR was selected as a lower dose for evaluation, along with the higher dexlansoprazole MR doses (60 mg and 90 mg) to assess efficacy and safety for both the symptomatic GERD and maintenance of healed EE studies.

Medical Officer Comments:

The sponsor's approach was a rational one and is consistent with dosing for other PPIs for this indication.

6.3.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

For the symptomatic GERD indication, the persistence of efficacy and/or tolerance effects were not formally assessed with subject daily diaries beyond the recommended 4-week treatment duration. However, in Studies T-GD05-137 and T-GD04-082, efficacy was demonstrated as early as the first 3 days and continued to increase throughout the 4-week Treatment Period (see Figures above).

Although the recommended dose, dexlansoprazole MR 30 mg, has not been studied in symptomatic GERD subjects beyond 4 weeks, dexlansoprazole MR doses of 60 mg and 90 mg have been studied for up to 12 months (Study T-GI04-088), during which time QOL and symptom severity were assessed via subject-reported PAGI-QOL and PAGI-SYM questionnaires, respectively. Data from this study can be considered supportive, given the similar efficacy observed in symptomatic GERD subjects treated with dexlansoprazole MR 30 mg, 60 mg, and 90 mg QD.

In this long-term study, improvement in QOL and reduction in symptom severity were observed in both the dexlansoprazole MR 60-mg QD and 90-mg QD treatment groups compared to baseline. This effect was demonstrated as early as the first assessment (Month 1), was sustained throughout the 12-month Treatment Period, and was similar for both doses in the subsets of subjects who completed the study and had a Month 12 Pagi-QOL or Pagi-SYM total score.

Medical Officer Comments:

(b) (4)

6.3.9 Additional Efficacy Issues/Analyses

Medical Officer Comments:

(b) (4)

(b) (4)

- The primary endpoint chosen by the sponsor is well-designed and appears to provide information to support the efficacy of dex in treating heartburn both during the daytime and nighttime. **(b) (4)**

Of the 5 approved prescription PPIs currently on the market, **(b) (4)** carries an indication for the treatment of **(b) (4)**. The review for rabeprazole for this indication reveals that the clinical studies were relatively small (316 patients total) and used a primary endpoint of “median time to onset of first 24h heartburn free interval (days).” Secondary endpoints included “median time in days to first nighttime heartburn-free interval,” and “average nighttime heartburn score change at Week 4.” **(b) (4)**

(the secondary endpoints chosen were “percentage of heartburn free daytime and/or nighttime periods over 4 weeks” and difference in daily mean daytime and nighttime heartburn scores.) **(b) (4)**

(b) (4)

(b) (4)

Given that the approval for (b) (4) was thus based on secondary endpoints of two small studies, and that the reviewer is unable to confirm what methodology was used to adjust for the multiplicity of examining these secondary endpoints (b) (4)

A scientific basis for granting a claim (b) (4) is equally elusive. The epidemiology of nocturnal GERD is not well-studied and experts have been unable even to agree on an accepted definition for the condition. Farup et al. proposed the following: nocturnal awakening by GERD symptoms, nocturnal awakening caused by coughing or choking, regurgitation of fluid or food and acidic/bitter taste, GERD symptoms while in the supine position, and morning awakening secondary to GERD symptoms.⁹ In contrast, Fass et al. suggest that nighttime heartburn should only be defined as “heartburn that awakens patients from sleep during the night.”¹⁰ The second definition is more restrictive, but focuses on the importance of GERD-related symptoms that occur during sleep as opposed to those which may occur while the patient is supine but awake.

Schoeman and Pasricha discuss that the symptoms of nocturnal reflux are not due solely to the patients’ supine position as is often supposed; rather, they are due largely to the numerous physiologic mechanisms which are altered during sleep, including decreased rate of swallowing, diminished salivary production, and reduced upper esophageal sphincter basal pressure.^{11, 12} This overall alteration in esophageal defense mechanisms leads to prolonged acid exposure at night, which is associated with increased risk of severe GERD manifestations, including erosive esophagitis, peptic stricture, Barrett’s esophagus and adenocarcinoma of the esophagus.¹³

Moreover, although the presence of nocturnal symptoms is important in that it can be a predictor of serious sequelae of GERD, (b) (4)

In truth, the prescribing physician intends to treat the underlying GERD by controlling acid production throughout the 24-hour period of a given day, and the once-daily timing of any PPI provides this 24-hour control.

Based on the above discussion, the reviewer recommends that the language of the indication be modified to “treatment of heartburn associated with non-erosive GERD.” Any further parsing of the underlying disease of GERD into (b) (4) (b) (4) for a labeling claim seems unnecessary based on the biopharmaceutical profile of the product and minimally clinically useful based on the current scientific understanding of the disease process.

Note: The reviewer's concerns with the sponsor's proposed language for the indication should not preclude the presentation of the primary efficacy findings in the Clinical Studies section of the label, since the drug did in fact meet its primary endpoint without difficulty.

7 Appendices

7.1 Literature Review/References

- 1) Fass R, et al. Nonerosive reflux disease-current concepts and dilemmas. *Am J Gast* 96: 303-314; 2001.
- 2) Fennerty M. Medical treatment of GERD in the managed care environment. *Semin Gast Dis* 8: 90-99; 1997.
- 3) Orlando R. The pathogenesis of GERD: the relationship between epithelial disease, dysmotility, and acid exposure. *Am J Gast* 92: 3S-5S; 1997.
- 4) Holloway R, et al. Symptomatic GER as a risk factor for esophageal adenocarcinoma. *NEJM* 340: 825-831; 1999.
- 5) Fennerty M, et al. The diagnosis and treatment of GERD in a managed care environment. Suggested disease management guidelines. *Arch Int Med* 156: 477-484; 1996.
- 6) Hillman L, et al. PPI therapy and the development of dysplasia in patients with Barrett's oesophagus. *Med J Aust* 180: 387-391; 2004.
- 7) Freston J. Therapeutic choices in reflux disease: defining the criteria for selecting a PPI. *Am J Med* 117: 14S-22S; 2004.
- 8) Medical Officer Review for NDA 20-973/SE1-009 (rabeprazole for sGERD)
- 9) Farup C., et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Int Med* 161: 1448-1456; 2001.
- 10) Fass R., et al. Predictors of nocturnal heartburn in a large population-based study. *Chest* 127: 1486-88; 2005.
- 11) Schoeman M., et al. Integrity and characteristics of secondary oesophageal peristalsis in patients with gastro-oesophageal reflux disease. *Gut* 36: 499-504; 1995.
- 12) Parischa P., et al. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. *Am J Med* 18: Suppl 3A; 2003.

Clinical Review
Keith B. St. Amand, MD
NDA 22-287
(b) (4) (dexlansoprazole)

- 13) Lagergren J., et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *NEJM* 340: 825-831; 1999.

7.2 Labeling Recommendations

Since significant safety concerns are pre-empting the approval of dexlansoprazole during this review cycle, the reviewer will not provide a line-by-line labeling review at this time. General labeling recommendations related to the efficacy of the product have been presented in the body of the review.

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Keith B St.Amand
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MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22287
Brand Name	(b) (4)
Generic Name	Dexlansoprazole (TAK-390MR)
Sponsor	TAP Pharm
Indication	Healing of erosive esophagitis (EE); maintenance of healed EE; and symptomatic GERD
Dosage Form	Tablet
Drug Class	Proton pump inhibitor
Therapeutic Dose	30, 60, (b) (4) mg qd
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Application Submission Date	28 Dec 2007
Review Classification	Standard NDA
Date Consult Received	8 Feb 2008
Clinical Division	DGP / HFD 180
PDUFA Date	28 Oct 2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS (b) (4)

No significant QT prolongation effect of (b) (4) (90 mg and 300 mg) was detected in this TQT study. The largest upper bounds of the (b) (4)-sided 90% CI for the mean difference between (b) (4) (90 mg and 300 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. The assay sensitivity of the study was established.

In this randomized, blinded, four-period crossover study, 40 healthy subjects received TAK-390MR 90 mg, TAK-390MR 300 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for TAK-390MR (90 mg and 300 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
TAK-390MR 90 mg	16	2.14	(-1.69, 5.98)
TAK-390MR 300 mg	6	1.77	(-1.78, 5.32)
Moxifloxacin 400 mg*	4	13.25	(10.07, 16.44)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment is 7.73 ms.

The suprathreshold dose of 300 mg (3.3-fold higher than therapeutic dose of 90 mg and 5-fold higher than therapeutic dose of 60 mg for moderate hepatic impairment patients) is adequate and will cover the highest expected clinical exposure scenario (C_{max} : 2-fold increase in CYP2C19 poor metabolizers, 2-fold increase in moderate hepatic impairment, and 1.5-fold increase with food).

Fridericia (QTcF) provided an adequate correction of QT. No systematic increase in $\Delta\Delta QTcF$ with increase in TAK-390MR concentrations was observed.

2 PROPOSED LABEL

The sponsor has proposed to include the following information regarding the TQT study in Section 12.2 (Pharmacodynamics):

“Effect on Cardiac Repolarization: A study was conducted to assess the potential of (b) (4) to prolong the QT/QTc interval in healthy adult subjects. (b) (4) doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QTc intervals compared to placebo.”

Reviewer’s Comments: Our suggestions for labeling are shown below. We defer final labeling decisions to the review division.

In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects received (b) (4) 90 mg, (b) (4) 300 mg, placebo, and a single dose of moxifloxacin 400 mg. There were no significant effects of (b) (4) on the QT interval.

3 BACKGROUND

Dexlansoprazole is a substituted benzimidazole that inhibits gastric acid secretion. It is the R-enantiomer of lansoprazole, which is a PPI that was approved in the US in 1995 for a variety of acid-related gastrointestinal disorders, including healing of erosive esophagitis (EE), maintenance of healed EE, and symptomatic GERD. TAP developed a dual delayed release formulation of dexlansoprazole, referred to as dexlansoprazole modified release (MR) in this submission.

3.1 MARKET APPROVAL STATUS

Dexlansoprazole MR has not been marketed in any country. Lansoprazole, the racemate of dexlansoprazole has been marketed for over 12 years with global patient exposure of over 432 million.

3.2 PRECLINICAL INFORMATION

Source Pharmacology Written summary (Module 2.6.2)

“The effects of dexlansoprazole (1, 10 and 100 μM) on action potential parameters in isolated canine Purkinje fibers were evaluated when the fibers were paced at 0.5 and 1 hertz (Module 2.6.3 Table 2.6.3.4; Study Number TAK-390MR/00018).

Dexlansoprazole at concentrations of 1 and 10 μM had no obvious effects on upstroke amplitude (UA), resting membrane potential (RMP), maximum rate of depolarization (MRD) or action potential duration at 60 and 90% repolarization (APD60 and APD90). At 100 μM , dexlansoprazole elicited statistically significant

reductions in MRD and APD. This suggests that at 100 μ M, dexlansoprazole may prolong the QRS duration and shorten the QT interval in the ECG. Based on the mean C_{max} value of approximately 2 μ g/ml observed after administration of 90 mg of dexlansoprazole MR for five days to healthy volunteers (Module 2.7.2; Study T-P104-071) and the 96% human plasma protein binding of dexlansoprazole (Module 2.7.2; Report number 6764-367), the safety margin range based on free drug is approximately 50 to 500 fold. In addition, intravenous administration of lansoprazole at 10 mg/kg in dogs resulted in a C_{max} of 11 μ g/ml (30 μ M) and did not cause any changes in ECG QT or PR intervals. Therefore, prolongation of the QRS duration and shortening of the QT interval are highly unlikely to occur in humans taking clinically relevant doses of dexlansoprazole MR.”

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety (Module 2.7.4)

“A total of 4794 subjects received at least 1 dose of dexlansoprazole MR in Phase 1 studies and in Phase 3 symptomatic GERD, healing of EE, maintenance of healed EE, and long-term safety studies. A total of 651 subjects have been exposed to dexlansoprazole MR doses of 30 mg, 60 mg, or 90 mg QD for 6 months ($\geq$ 24 weeks) and 203 subjects have been exposed to doses of either 60 mg QD or 90 mg QD for at least 1 year ($\geq$ 48 weeks).

“In all Phase 3 studies combined, the most frequently reported treatment-emergent adverse event among all dexlansoprazole MR subjects and lansoprazole 30-mg QD subjects was Diarrhoea (Excl Infective). Upper Respiratory Tract Infections; Gastrointestinal and Abdominal Pains (Excl Oral and Throat); Nausea and Vomiting Symptoms; Headaches NEC; and Flatulence, Bloating, and Distension were also common in the active treatment groups.

“In all Phase 3 studies combined, the numbers of subjects per 100 PM with treatment-emergent potential cardiovascular adverse events were 1.79, 1.93, 1.61, 1.41, and 1.72 in the placebo, dexlansoprazole MR 30-mg QD, 60-mg QD, and 90-mg QD, and lansoprazole 30-mg QD treatment groups, respectively (Table 2.7.p). No statistically significant differences between any of the dexlansoprazole MR treatment groups and a comparator group (placebo or lansoprazole 30-mg QD) were observed for the overall incidence of treatment-emergent potential cardiovascular adverse events. No dose response was observed for the incidence of any specific potential cardiovascular adverse event.”

Reviewer’s Comment: There are no reports of adverse events related to QT prolongation, i.e. sudden cardiac death, seizures or significant ventricular arrhythmias.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of dexlansoprazole’s clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted the study report for T-P104-092, electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Randomized, Double-Blind, Four-Period Crossover Study to Assess the Effects on the Cardiac QT Interval of a Single Dose of TAK-390MR (90 mg and 300 mg) with a Placebo Control and Avelox 400 mg as an Active Control in Healthy Subjects.

4.2.2 Protocol Number

T-P104-092

4.2.3 Study Dates

Jan 2005 – Feb 2005

4.2.4 Objectives

The objectives of this study were to identify any potential effects of the modified-release formulation of TAK-390 (TAK-390MR) on QT interval and safety at single doses up to 300 mg, as compared to placebo, in healthy subjects and to compare the pharmacokinetic profiles of single doses of 90 mg and 300 mg of TAK-390MR in the same subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4-sequence, crossover design with four dosing occasions. Each dosing occasion will be followed by a 5-day washout period.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

On each dosing day (Day 1 of each crossover period), subjects were administered dosing regimens according to the sequence they were assigned. During each crossover period, 10 subjects were to receive each of the dosing regimens identified below.

Regimen	Drug and Dose
A	A single, oral dose of 90 mg of TAK-390MR administered as 1 capsule containing 90 mg of TAK-390MR and 3 capsules of placebo (blinded).
B	A single, oral dose of 300 mg of TAK-390MR administered as two 60-mg capsules and two 90-mg capsules of TAK-390MR (blinded).
C	A single, oral dose of placebo for TAK-390MR administered as 4 placebo capsules (blinded).
D	A single, oral dose of 400 mg of Avelox administered as one 400-mg tablet (open label).

Sponsor' Table 9.1.a on page 32 of TAK-390MR: STUDY T-P104-092 Clinical Study Report

4.2.6.2 Sponsor's Justification for Doses

The 90-mg dose of TAK-390MR was chosen because it represents the upper end of the dosing range being considered for future clinical efficacy studies.

The higher dose of 300 mg of TAK-390MR was chosen to provide a "substantial multiple" of the anticipated maximum therapeutic exposure, as suggested in the FDA guideline on evaluation of non-antiarrhythmic drugs for QT/QTc prolongation. The 300-mg dose of TAK-390MR is 3.33 to 10.0 times higher than the potential clinical doses of 30 to 90 mg.

Reviewer's comments: The proposed supra-therapeutic dose of 300 mg (3.3-fold higher than therapeutic dose of 90 mg and 5-fold higher than therapeutic dose of 60 mg for moderate hepatic impairment patients) is adequate and will cover the highest expected clinical exposure scenario (C_{max} : 2-fold increase in CYP2C19 poor metabolizers, 2-fold increase in moderate hepatic impairment, and 1.5-fold increase with food).

4.2.6.3 Instructions with Regard to Meals

Doses were administered following a minimum 10 hr fast.

4.2.6.4 ECG and PK Assessments

Table 2: Sampling Schedule

Study Day	-1	1	2-5
Intervention	No treatment (Baseline)	Single dose	No treatment (Washout)
12-Lead ECGs	Record ECGs ^{###}	Record ECGs ^{###}	None recorded
PK Samples for drug	None collected	Collected ^{###}	None collected

^{###}0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 23.75 hr post dosing.

Reviewer's comment: The ECG and PK assessments are adequate to capture the QT effect at peak TAK-390 concentrations (t_{max} =4-5 hr).

4.2.6.5 Baseline

The sponsor used the same day pre-dose QTc values as the baseline.

4.2.7 ECG Collection

(b) (4) monitors (b) (4) were used to obtain the 24-hour Holter recordings on Day -1 and Day 1 at the time points specified above to assess the effects of study drug on the QT interval. At each of the times specified for collection of ECGs for QT interval assessment, subjects were in a supine position for approximately 20 minutes bracketing the time point.

From the Holter recording obtained during the 15-minute observation window of each specified time point, 3 distinct ECGs were extracted from the continuous Holter data by the core lab.

The central, independent cardiologists (b) (4) read all ECGs using digital, on-screen systems. ECGs for an individual subject could have been read by multiple cardiologists. The central reviewers, who were blinded to treatment and sequence, read and interpreted each ECG for rhythm, rate, intervals, and morphology using Digitography.

12-lead safety ECGs were also obtained at each subject's bedside at specified times after dosing on Day 1 of each period.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Forty subjects (33 males, 7 females), between 18-50 yrs of age, with a normal baseline ECG and BMI between 18-30 kg/m² were enrolled in the study. Thirty-four subjects completed all 4 dosing regimens, and 6 subjects prematurely discontinued from the study. Among the 6 subjects, 4 subjects discontinued due to protocol violation (positive urine drug screen), 1 subject discontinued due to personal reasons, and 1 subject discontinued due to an adverse event.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary analysis was performed on all time-points for QTcF using an analysis of variance (ANOVA) model with treatment, sequence, period as fixed effects, and subject as a random effect. The upper bounds of the one-sided 95% CIs for the mean differences between TAK-390MR (doses of 90 mg and 300 mg) and placebo in QTcF at each time point were below 10 ms. The largest upper bound for TAK-390 MR 90 mg and 300 mg of the one-sided 95% CIs were 6.8 ms and 7.0 ms, respectively. Table 3 presents ANOVA model analysis results in QTcF. The sponsor used Avelox 400 mg as the positive control in the study. The mean change from baseline in QTcF interval was ≥ 5.0 ms at 13 of 19 post dosing time points after administration for Avelox 400 mg.

Table 3: Mixed Model Analysis in QTcF

	TAK-390MR 90 MG vs. PLACEBO		TAK-390MR 300 MG vs. PLACEBO		AVELOX 400 MG vs. PLACEBO	
	Differences ^{&}	Upper Bound of 95% One-sided C.I. [§]	Differences ^{&}	Upper Bound of 95% One-sided C.I. [§]	Differences ^{&}	Upper Bound of 95% One-sided C.I. [§]
Fridericia QT Interval (msec)						
0.5 hr	1.9	5.6	-0.1	3.5	2.7	6.3
1 hr	-0.9	2.7	-1.9	1.6	7.1	10.6
1.5 hr	-3.6	0.1	-2.2	1.4	8.8	12.4
2 hr	-2.4	1.4	0.4	4.0	8.7	12.4
2.5 hr	-0.7	3.5	0.0	4.1	9.5	13.6
3 hr	2.6	6.5	0.9	4.8	11.4	15.3#
4 hr	-0.2	3.4	-1.1	2.4	11.5	15.1
5 hr	-0.6	2.7	1.5	4.7	5.9	9.2
5.5 hr	1.5	5.6	3.0	7.0#	7.8	11.9
6 hr	1.3	5.1	0.3	3.9	6.9	10.5
6.5 hr	3.6	6.8	0.6	3.8	8.4	11.5
7 hr	-0.3	3.4	-1.1	2.5	6.3	9.9
7.5 hr	3.3	6.8#	1.4	4.9	10.9	14.2
8 hr	-1.7	2.1	-0.6	3.1	6.0	9.7
10 hr	-0.9	3.1	-3.0	0.9	0.6	4.5
12 hr	1.4	4.8	-2.7	0.6	4.8	8.1
15 hr	1.9	5.6	2.8	6.5	9.5	12.2
23.75 hr	1.4	4.9	0.4	3.9	5.5	9.0
7 Days ^{&}	-1.3	3.4	-1.3	3.6	0.0	4.9

& Difference in the least-square means of the change from baseline, from the ANOVA model at each time point.
 § The 95% one-sided confidence interval is for the difference in the least-square means of the change from baseline.
 # The maximum of the upper bound of the 95% one-sided confidence interval over all the time points.
 & ECGs were taken at 15 minutes prior to the dosing of next regimen. ECGs taken at -24.25 hours on Day -1 Period 1 were used as the baseline.

Sponsor' Table 14.2.9.2 on page 74 of TAK-390MR: STUDY T-P104-092 Clinical Study Report

Reviewer's comments: The sponsor did not present the lower confident interval for the comparison between Avelox and Placebo in this study report. To establish assay sensitivity, at least one lower bound (after multiply endpoint adjustment) should be greater than 5 ms.

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4.2.8.2.2 Categorical Analysis

The number and percentage of subjects with QT, QTcF, or QTcB interval shifts (<30 ms, 30 to <60 ms, and ≥60 ms) will be summarized by regimen.

The number and percentage of subjects with QT, QTcF, or QTcB intervals ≤450 ms, >450 ms and ≤480 ms, >480 ms and ≤500 ms, and >500 ms will be tabulated by regimen.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study.

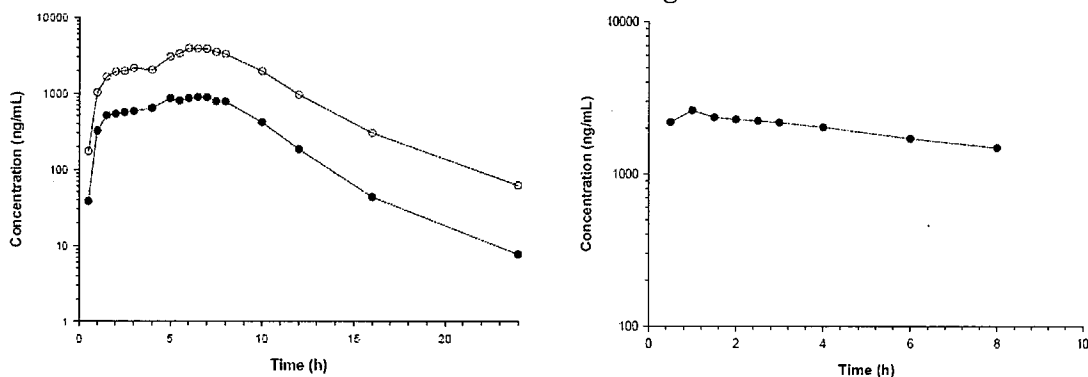
One subject (129) discontinued due to an elevated AST on Study day 20 at the end of the washout period following period 3 (placebo administration). He had earlier received TAK 390MR 300mg and Moxifloxacin 400 mg.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The mean plasma TAK-390 concentration versus time curves following single, oral doses of 90 mg or 300 mg of TAK-390MR are shown in Figure 1.

Figure 1: Plasma TAK-390 concentration versus time profiles presented on a log-linear scale. (Left) TAK-390MR (solid dots = 90 mg, open circles = 300 mg), (Right) Moxifloxacin 400 mg.



Sponsor' Figure 14.2.17.1-2 on page 370-371 of TAK-390MR: STUDY T-P104-092 Clinical Study Report

Mean pharmacokinetic parameter estimates for subjects with complete data for TAK-390 Regimens A (90-mg TAK-390MR) and B (300-mg TAK-390MR) are summarized in Table 4.

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Table 4: Mean Pharmacokinetic Parameter Estimates for TAK-390 Following Administration of Single, Oral Doses of 90 mg (Regimen A) or 300 mg (Regimen B) of TAK-390MR.

Measure	Mean Pharmacokinetic Parameter					
	t_{max} (h)	C_{max} (ng/mL)	AUC_{∞} (ng·h/mL)	CL/F (L/h)	V_z/F (L)	$t_{1/2z}$ (h) ^a
TAK-390MR 90 mg (Regimen A)						
N ^b	35	35	35	35	35	35
Mean	5.10	1471	7415	16.9	35.9	1.51
%CV	42	54	58	60	35	NA
TAK-390MR 300 mg (Regimen B)						
N ^b	35	35	35	35	35	35
Mean	4.98	5392	30641	14.8	41.7	1.95
%CV	46	50	65	73	59	NA

a Harmonic mean.

b Number of subjects with complete data.

Sponsor' Table 11.4.h on page 97 of TAK-390MR: STUDY T-P104-092 Clinical Study Report

Mean plasma moxifloxacin concentration versus time curves following a single, oral dose of 400 mg of Avelox are shown in Figure 1 (right). Mean pharmacokinetic parameter estimates for subjects with available data for moxifloxacin are presented in Table 5.

Table 5: Mean Pharmacokinetic Parameter Estimates for Moxifloxacin Following Administration of a Single, Oral Dose of 400 mg of Avelox (Regimen D).

Measure	Mean Pharmacokinetic Parameter		
	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)
N ^a	37	37	37
Mean	1.47	3141	15561
%CV	75	30	20

a Number of subjects with available data for moxifloxacin.

Sponsor' Table 11.4.i on page 98 of TAK-390MR: STUDY T-P104-092 Clinical Study Report

4.2.8.4.2 Exposure-Response Analysis

No exposure-response analysis was performed by the sponsor.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

QTcF Analysis

The statistical reviewer calculated the raw mean difference of QTcF between the study drug and placebo using the same day pre-dose value as the baseline as well as the 2-sided 90% confidence interval. The results are summarized in Table 6 and Table 7 for TAK-390MR 90 mg and 300 mg, respectively. The upper bounds of the two-sided 90% CIs for the mean differences of QTcF between TAK-390MR and placebo for both doses after pre-dose baseline adjustment at each time point are below 10 ms. The largest upper bounds for TAK-390MR 90 mg and 300 mg are 5.98 ms at 16 hours and 5.32 ms at 6 hours after

dosing, respectively. Table 8 summarizes the results of the mean difference between Avelox 400 mg and placebo in QTcF with and without multiplicity adjustments. Without multiplicity adjustment, the largest lower bound for Avelox 400 mg is 10.07 ms at 4 hours after dosing. After adjusted for 18 post-baseline time points, the largest lower bound for Avelox is 7.73 ms at 4 hours after dosing. Figure 2 presents the time-course of $\Delta\Delta$ QTcF for TAK-390MR 90 mg, TAK-390MR 300 mg and Avelox 400 mg.

Table 6: Analysis of QTcF difference between 90mg TAK-390MR and placebo for Day 1

Time (hr)	N	Δ QTcF(SD)	Δ Placebo(SD)	$\Delta\Delta$ QTcF	
		TAK-390MR 30mg	Placebo	Diff(SD)	90% CI
0.5	34	-3.44 (6.19)	-1.52 (6.34)	-1.92 (9.28)	(-4.62, 0.77)
1	34	-1.36 (7.71)	-0.99 (5.90)	-0.37 (9.42)	(-3.11, 2.36)
1.5	34	-2.90 (8.18)	-0.30 (6.71)	-2.60 (11.32)	(-5.88, 0.69)
2	34	-1.75 (6.72)	-0.31 (7.61)	-1.43 (11.37)	(-4.73, 1.87)
2.5	34	-1.91 (6.67)	-0.83 (7.75)	-1.08 (9.56)	(-3.85, 1.70)
3	34	-1.86 (6.14)	-1.58 (9.18)	-0.28 (10.42)	(-3.31, 2.74)
4	34	-2.94 (6.46)	-3.53 (8.05)	0.59 (10.19)	(-2.37, 3.55)
5	34	-8.50 (9.31)	-7.02 (10.77)	-1.48 (13.06)	(-5.27, 2.31)
5.5	34	-9.34 (9.32)	-7.88 (11.83)	-1.46 (11.91)	(-4.92, 1.99)
6	34	-8.16 (9.38)	-9.89 (10.06)	1.74 (13.00)	(-2.04, 5.51)
6.5	34	-9.50 (10.73)	-8.82 (7.79)	-0.68 (12.20)	(-4.22, 2.86)
7	34	-8.34 (9.67)	-9.16 (8.03)	0.81 (10.15)	(-2.13, 3.76)
7.5	34	-8.71 (10.78)	-8.93 (7.83)	0.23 (11.30)	(-3.05, 3.51)
8	33	-7.75 (9.67)	-8.16 (9.98)	0.41 (11.92)	(-3.10, 3.93)
10	33	-5.26 (9.47)	-5.95 (8.22)	0.69 (8.83)	(-1.92, 3.29)
12	33	-5.67 (7.87)	-5.41 (7.79)	-0.25 (8.80)	(-2.85, 2.34)
16	33	1.56 (11.24)	-0.59 (9.37)	2.14 (13.01)	(-1.69, 5.98)
23.75	34	-3.24 (6.94)	-3.83 (7.41)	0.59 (10.76)	(-2.53, 3.72)

Note: Δ QTcF: Mean change from baseline in QTcF interval.
 $\Delta\Delta$ QTcF: Placebo adjusted, mean change from baseline in QTcF
diff: TAK-390MR 90mg - placebo (after baseline adjustment)

Table 7: Analysis of QTcF difference between 300mg TAK-390MR and placebo for Day 1

Time (hr)	N	Δ QTcF(SD)	Δ Placebo(SD)	$\Delta\Delta$ QTcF	
		TAK-390MR 300mg	Placebo	Diff(SD)	90% CI
0.5	38	-2.17 (8.56)	-1.46 (6.02)	-0.71 (10.08)	(-3.47, 2.05)
1	38	-1.26 (8.18)	-1.06 (5.60)	-0.20 (8.36)	(-2.49, 2.09)
1.5	38	-2.74 (8.44)	-0.02 (6.46)	-2.72 (11.12)	(-5.76, 0.33)
2	38	-0.96 (9.50)	-0.44 (7.23)	-0.53 (11.81)	(-3.76, 2.70)
2.5	38	-2.78 (7.92)	-0.94 (7.34)	-1.84 (9.80)	(-4.52, 0.84)
3	38	-3.54 (8.06)	-1.44 (8.79)	-2.10 (12.15)	(-5.42, 1.23)
4	38	-4.02 (9.21)	-3.80 (7.88)	-0.22 (12.33)	(-3.59, 3.15)
5	37	-6.77 (10.21)	-6.93 (10.51)	0.15 (11.80)	(-3.12, 3.43)
5.5	37	-8.65 (10.03)	-7.80 (11.41)	-0.85 (11.40)	(-4.01, 2.32)
6	37	-8.22 (11.53)	-9.99 (9.86)	1.77 (12.79)	(-1.78, 5.32)
6.5	37	-9.68 (10.09)	-8.68 (7.75)	-1.01 (11.15)	(-4.10, 2.08)
7	38	-10.5 (9.97)	-8.82 (7.89)	-1.72 (10.42)	(-4.57, 1.13)
7.5	38	-10.7 (9.70)	-8.61 (7.70)	-2.07 (10.30)	(-4.89, 0.75)
8	38	-9.75 (10.54)	-8.18 (10.31)	-1.58 (13.60)	(-5.30, 2.14)
10	38	-8.53 (11.23)	-6.24 (8.27)	-2.29 (10.60)	(-5.19, 0.61)
12	38	-8.46 (7.78)	-6.13 (8.26)	-2.33 (8.93)	(-4.78, 0.11)
16	38	-1.61 (11.03)	-0.96 (8.83)	-0.65 (12.59)	(-4.10, 2.80)
23.75	37	-3.51 (9.61)	-3.36 (7.47)	-0.15 (12.51)	(-3.62, 3.32)

Note: Δ QTcF: Mean change from baseline in QTcF interval.
 $\Delta\Delta$ QTcF: Placebo adjusted, mean change from baseline in QTcF
diff: TAK-390MR 300mg - placebo (after baseline adjustment)

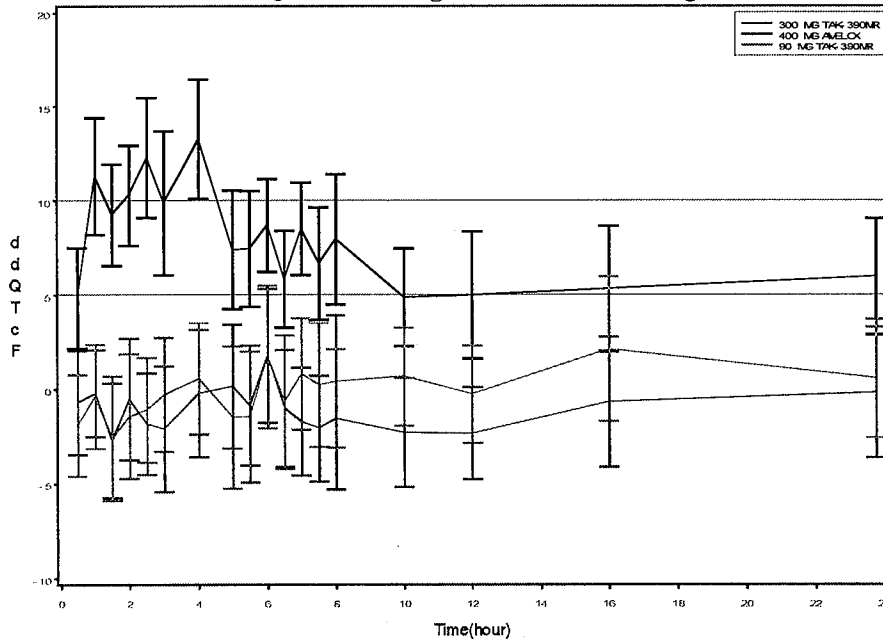
Table 8: Analysis of QTcF difference between Avelox 400mg and Placebo for Day 1

Time (hr)	N	Δ QTcF(SD)	Δ Placebo(SD)	Diff (SD)	$\Delta\Delta$ QTcF	
		Avelox	Placebo		90% CI	Adjusted 90% CI*
0.5	35	3.16 (6.97)	-1.69 (6.18)	4.85 (9.34)	(2.18, 7.52)	(0.22, 9.48)
1	35	10.09 (8.63)	-1.21 (5.80)	11.30 (10.84)	(8.20, 14.39)	(5.92, 16.67)
1.5	35	9.12 (6.93)	-0.13 (6.69)	9.26 (9.37)	(6.58, 11.94)	(4.61, 13.90)
2	35	9.57 (8.12)	-0.70 (7.37)	10.28 (9.27)	(7.63, 12.93)	(5.68, 14.87)
2.5	34	11.06 (7.61)	-1.23 (7.52)	12.28 (10.93)	(9.11, 15.46)	(6.78, 17.79)
3	34	8.11 (8.62)	-1.78 (9.04)	9.89 (13.15)	(6.08, 13.71)	(3.27, 16.52)
4	34	9.10 (7.93)	-4.16 (7.99)	13.25 (10.96)	(10.07, 16.44)	(7.73, 18.78)
5	35	-0.22 (7.75)	-7.62 (10.27)	7.40 (10.98)	(4.26, 10.54)	(1.96, 12.84)
5.5	35	-0.86 (7.96)	-8.30 (11.52)	7.45 (10.69)	(4.39, 10.50)	(2.15, 12.74)
6	35	-2.22 (7.26)	-10.9 (9.16)	8.69 (8.63)	(6.22, 11.15)	(4.41, 12.96)

6.5	35	-3.50 (7.59)	-9.34 (7.35)	5.84 (8.96)	(3.28, 8.40)	(1.40, 10.28)
7	35	-1.38 (8.26)	-9.89 (7.09)	8.50 (8.54)	(6.06, 10.95)	(4.27, 12.74)
7.5	35	-2.84 (7.77)	-9.50 (7.28)	6.67 (10.39)	(3.70, 9.64)	(1.52, 11.82)
8	35	-1.40 (8.63)	-9.37 (9.51)	7.97 (12.07)	(4.52, 11.42)	(1.99, 13.95)
10	35	-2.09 (8.74)	-6.95 (8.17)	4.87 (9.02)	(2.29, 7.44)	(0.40, 9.34)
12	35	-1.88 (10.52)	-6.88 (8.10)	5.00 (11.76)	(1.64, 8.36)	(-0.83, 10.83)
16	34	3.80 (10.11)	-1.54 (8.65)	5.34 (11.44)	(2.02, 8.66)	(-0.42, 11.10)
23.75	35	2.00 (7.27)	-3.99 (7.11)	5.99 (10.82)	(2.89, 9.08)	(0.62, 11.35)

*CIs are adjusted with 18 post-baseline time points;
Diff: Avelox - placebo (after baseline adjustment)

Figure 2: Time Course $\Delta\Delta\text{QTcF}$ for 90mg TAK-390MR, 300mg TAK-390MR and 400mg Avelox



Categorical Analysis

The Categorical analysis results are shown in Table 9. No subject's QTcF was above 480 ms. No subject's ΔQTcF was above 60 ms.

Table 9: Frequency for QTcF and Absolute Δ QTcF

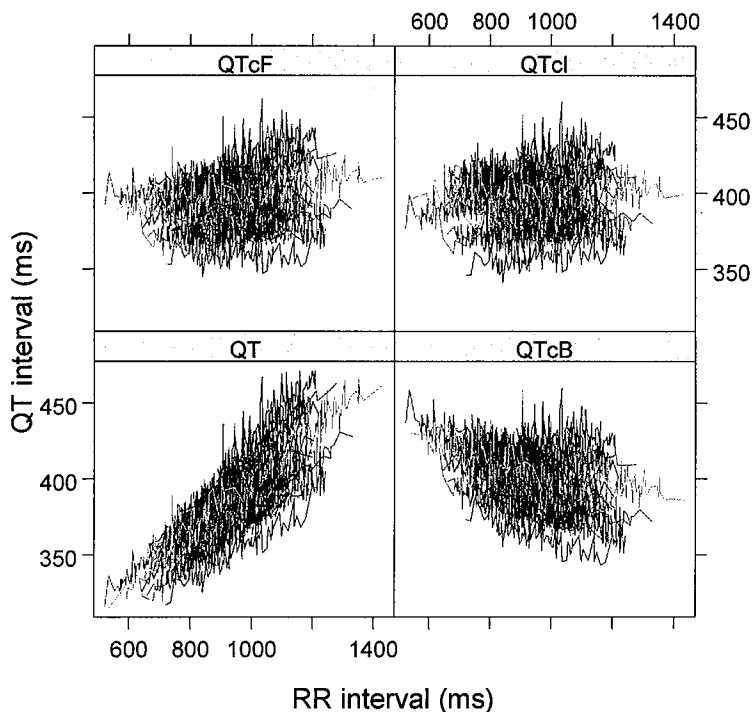
Category	Treatment	# of Subjects	total # Subjects	% of Subjects
450ms $\leq$ QTcF<480 ms	Placebo	0	37	0.0%
	400mg Avelox	1	36	2.8%
	90 mg TAK-390MR	2	34	5.9%
	300mg TAK-390MR	0	38	0.0%
30ms $\leq$ Δ QTcF < 60 ms	Placebo	5	37	3.2%
	400mg Avelox	6	37	13.5%
	90 mg TAK-390MR	6	34	14.7%
	300mg TAK-390MR	8	38	21.2%

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

5.2.1 QT Corrections

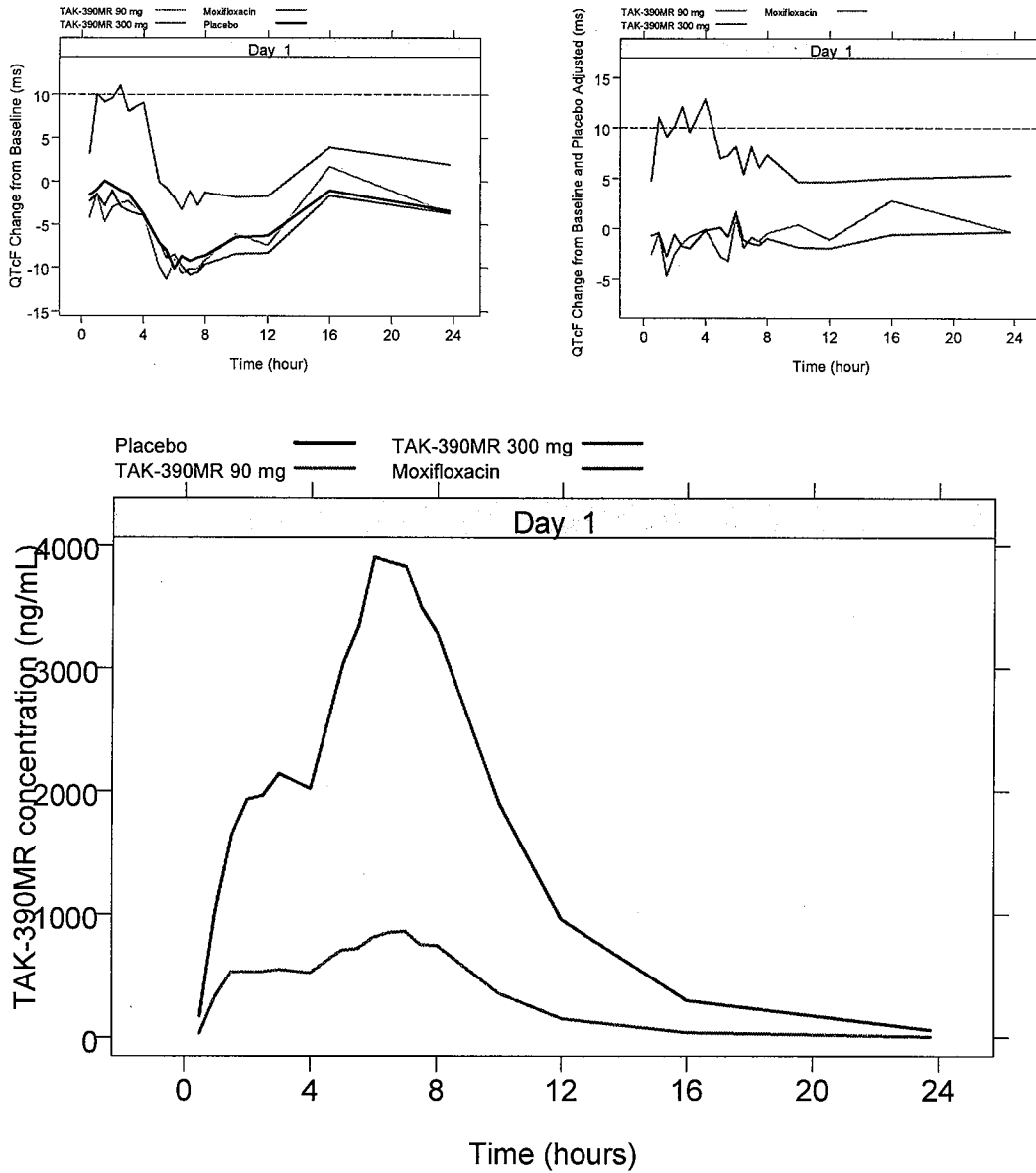
The observed QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI). QTcF is adequate to correct for the heart rate effect on QT.

Figure 3. QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line).



5.2.2 QTcF and TAK-390MR Concentration Time Profiles

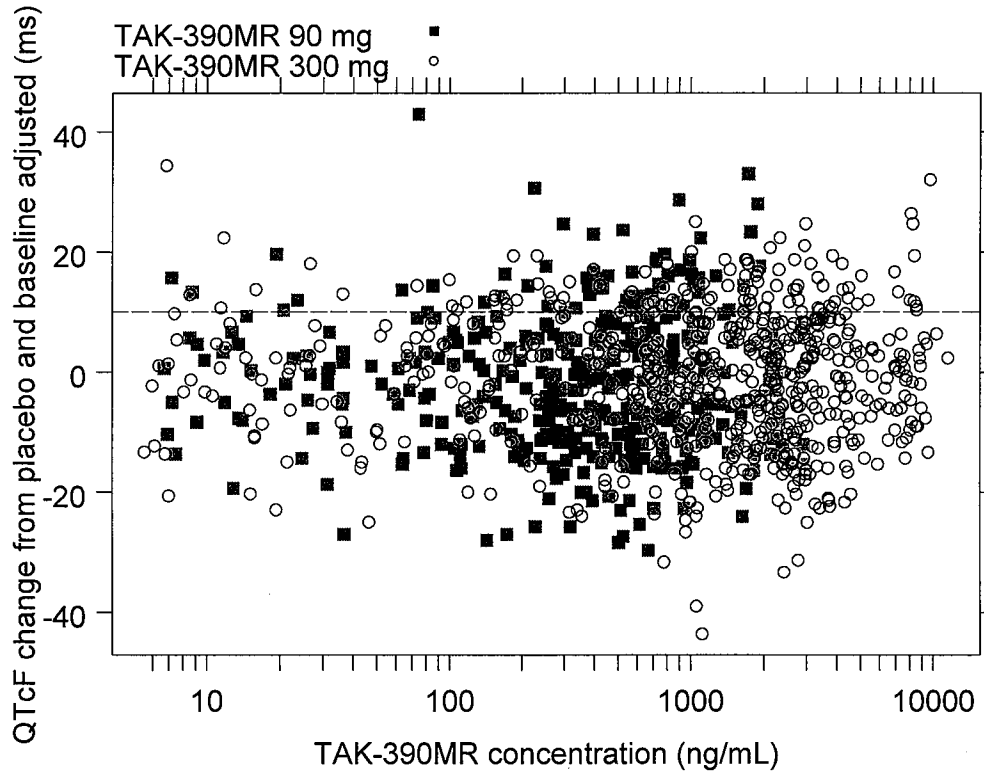
Figure 4. Mean Δ QTcF (change from baseline) (top left), $\Delta\Delta$ QTcF (placebo-adjusted change from baseline) (top right), TAK-390MR concentration (bottom) time profiles for TAK-390MR 90 mg (blue line), TAK-390MR 300 mg (red line), moxifloxacin (green line), and placebo (black line).



5.2.3 TAK-390MR Concentration-QTcF Analysis

The relationship between $\Delta\Delta$ QTcF and TAK-390MR concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5. $\Delta\Delta$ QTcF vs. TAK-390MR concentration.



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5.3 CLINICAL ASSESSMENTS

5.3.1 Safety Assessment

None of the events identified to be of clinical importance per the ICH E14 guidelines i.e. syncope, seizure, sudden cardiac death and significant ventricular arrhythmia occurred in this study.

5.3.2 ECG assessments

Waveforms initially submitted to the ECG warehouse read by (b) (4) were initially reviewed by the QT-IRT clinical reviewer. The QT-IRT was concerned that the ECGs were annotated in multiple leads within same and adjacent time points. On review of the ECGs, annotations were made in waveforms with low T wave amplitude, and baseline and on-treatment ECGs were not based on the same lead.

The ECG warehouse computes a comparison between the VERITAS™ algorithm determination of both QRS-onset and T-offset for an individual beat with the QRS-onset and T-offset annotation supplied. Disagreement with the algorithm (positive or negative QT bias) is ranked to highlight differences. In this case, more than 8% of ECGs had significant QT bias. Also, the distribution for QT bias was broad with a significant skew to the left compared to other studies that the QT-IRT had reviewed.

Following a T-con with the sponsor on 3/19/08, the sponsor agreed to re-interpret all the ECGs from this study (b) (4) and re-analyze the results.

Waveforms re-submitted to the ECG warehouse were reviewed. In this submission, Lead II was the primary lead with V5 as back-up lead. Over 96% of ECGs were annotated in the primary lead. According to ECG warehouse statistics, 6% of ECGs had significant QT bias. The mean QT bias and SDs were similar, when the QT-IRT analyzed this by treatment group. Hence, ECG interpretation appears acceptable in this re-submission.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Therapeutic doses of dexlansoprazole MR are 30, 60 (b) (4) once daily. The maximum recommended dose (b) (4) once daily for up to 8 weeks.	
Maximum tolerated dose	The maximum tolerated dose of dexlansoprazole has not been established in humans. A NOAEL dose of 5 mg/kg has been established for dogs, and 15 mg/kg for rats.	
Principal adverse events	There were no dose limiting adverse events. The most frequent ($\geq 5\%$) treatment emergent adverse events across all Phase 3 studies were upper respiratory tract infection and diarrhea (ISS, Appendix 12.9, Statistical Table 3.6.2.1).	
Maximum dose tested	Single Dose	300 mg
	Multiple Dose	120 mg once daily for 5 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean C_{max} (%CV): 5392 ng/mL (50) Mean AUC_{∞} (%CV): 30641 ng·h/mL (65)
	Multiple Dose	Mean C_{max} (%CV): 2973 ng/mL (44) Mean AUC_{24} (%CV): 17818 ng·h/mL (47)
Range of linear PK	Following administration of single 30 to 300 mg or multiple once daily 30 to 120 mg dexlansoprazole MR doses to healthy subjects, mean dexlansoprazole C_{max} and AUC values increased in an approximately dose proportional manner over the entire dose range.	
Accumulation at steady state	There is no dexlansoprazole accumulation at steady state.	
Metabolites	There are no active metabolites of dexlansoprazole. Tentatively identified metabolites in human plasma, urine and feces include: 5-glucuronyloxy dexlansoprazole, 5-hydroxy dexlansoprazole, dexlansoprazole sulfone, 5-sulfonyloxy dexlansoprazole sulfide, 4-sulfonyloxy dexlansoprazole sulfide, 5-hydroxy dexlansoprazole sulfone, 4-hydroxy dexlansoprazole sulfide, dexlansoprazole sulfide, 5-hydroxy dexlansoprazole sulfide, 5-glucuronyloxy dexlansoprazole sulfide, 4-sulfonyloxy dexlansoprazole, 2-S-N-acetylcysteinyl benzimidazole, and 2-S-N-acetylcysteinyl hydroxybenzimidazole. In study T-P106-141 in which subjects received [^{14}C]dexlansoprazole, dexlansoprazole was shown to be the major circulating component in the plasma of both CYP2C19 extensive metabolizers (EM) and a CYP2C19 poor metabolizer (PM). The 2 major circulating oxidative metabolites (5-hydroxy dexlansoprazole and dexlansoprazole sulfone) together accounted for approximately 6% of circulating radioactivity in EMs, and 17.5% in the PM subject	

Absorption	Absolute/Relative Bioavailability	The absorption of dexlansoprazole from the gastrointestinal tract is estimated to be at least 76% based on the recovery of [¹⁴ C]dexlansoprazole in the feces following oral administration of [¹⁴ C]dexlansoprazole.
	Tmax	- Following single or multiple 30, 60 or 90 mg once daily dexlansoprazole MR doses, median dexlansoprazole t_{max} values were 4 to 5 hours (range: 1 to 24 hours). - t_{max} values for 2 oxidative metabolites of dexlansoprazole were determined in 2 Phase 1 studies (T-P105-119 and T-P105-115). Median metabolite 5-hydroxy dexlansoprazole t_{max} values following a single 60 mg dexlansoprazole MR dose were 4.75 to 5.25 hours (range: 1.0 to 10 hours). Median metabolite dexlansoprazole sulfone t_{max} values were 1.75 to 5.0 hours (range: 1.0 to 14.0 hours).
Distribution	Vd/F or Vd	Following single or multiple once daily 30, 60 or 90 mg dexlansoprazole MR doses, mean dexlansoprazole Vd/F values ranged from approximately 24 to 40 L, with %CVs ranging from 49-89.
	% bound	Dexlansoprazole is approximately 96.1%-98.8% bound in plasma, primarily to albumin.
Elimination	Route	- Dexlansoprazole is extensively and almost completely metabolized in the liver to inactive metabolites by oxidation, reduction, and subsequent formation of sulfate, glucuronide, and glutathione conjugates. - Following administration of a [¹⁴C]dexlansoprazole dose, approximately 51% of the administered radioactivity is recovered in the urine, and 48% in the feces. No parent drug is recovered in the urine.
	Terminal t _{1/2}	- Following single or multiple once daily 30, 60 or 90 mg dexlansoprazole MR doses, mean dexlansoprazole terminal t_{1/2} values ranged from approximately 1.7 to 2.6 hours, with %CVs ranging from 45 to 99. - Terminal t_{1/2} values for the 2 oxidative metabolites of dexlansoprazole were determined in a Phase 1 Effect of Age and Gender study (T-P105-119). Mean metabolite 5-hydroxy dexlansoprazole terminal t_{1/2} values following a single 60 mg dexlansoprazole MR dose ranged from approximately 2.1 to 3.2 hours, with %CVs ranging from 41 to 50. Mean metabolite dexlansoprazole sulfone terminal t_{1/2} values ranged from approximately 2.4 to 3.6 hours, with %CVs ranging from 23 to 68.
	CL/F or CL	Following single or multiple once daily 30, 60 or 90 mg dexlansoprazole MR doses, mean dexlansoprazole CL/F values ranged from approximately 5.2 to 15.7 L/h, with %CVs ranging from 46 to 120.

6.2 TABLE OF STUDY ASSESSMENTS

Table 9.5.a Schedule of Assessments

Procedure	Screening Visit ^a		Days of Each Period ^b					Unscheduled Visit ^d
	Day -28 to Day -2 ^e	Day -2 ^e	Day -1	Day 1	Day 2	Day 2 Period 4/Premature Discontinuation		
Confinement		X	X	X	X ^c	X		
Informed Consent/HIPAA Authorization Form ^f	X							
Complete Social History	X							
Complete Medical History	X							
Medical History Update		X						
Complete Physical Examination	X	X				X		
Brief Physical Examination			X ^g		X ^c		X	
Body Weight and Height	X	X ^h				X ^h		
Vital Signs ⁱ	X	X	X	X	X ^c	X	X	
Electrocardiogram ^j	X	X	X	X		X	X	
Fasting Laboratory Evaluation ^k	X	X	X ^l		X ^c	X		
Pregnancy Test (females only) ^l	X	X	X ^l			X		
Drug, Alcohol, and Cotinine Screen	X	X	X ^o					
HIV and Hepatitis B and C	X							
Administration of Study Drug ^m				X				
24-Hour Blood Sampling for Pharmacokinetics ⁿ				X				
Adverse Events ^o	X	X	X	X	X	X	X	
Concomitant Medication Assessment	X	X	X ^o				X	

a Screening procedures were to be performed within 28 days prior to administration of the first dose of study drug (Day 1 of Period 1).

b There was a washout interval of at least 5 days between doses in successive periods.

c Period 1 only.

d Other study procedures at an unscheduled visit could be done at the discretion of principle investigator.

e Periods 1-3 only.

f Before any study-specific procedures were performed.

g Periods 2-4 only.

h Excluding height.

i Obtained at the Screening Visit, upon confinement, and upon rising in the morning during confinement.

j A screening ECG was obtained at the Screening Visit and on Day -2 of Period 1. Baseline ECGs were obtained on Day -1 of Period 1 using a 24-hour Holter monitor (mimicking the timepoints for ECGs and resting periods on Day 1 of Period 1) and on Day 1 of each period 15 minutes prior to dosing at (0 hour), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 23.75 hours after dosing. Single bedside safety 12-lead ECGs were collected at 1.5, 3, 5, and 6.5 hours after dosing on Day 1 of each period, and corresponding baseline safety ECGs were obtained on Day -1 of Period 1 at times mimicking those on Day 1.

k Obtained after a minimum 8-hour fast.

l A serum pregnancy test was done on all females at the Screening Visit, on Day -2 of Period 1, Day -1 of Periods 2 through 4, or if a female subject prematurely discontinued from the study.

m Study drug was administered beginning at approximately 0800 hours.

n For blinded regimens, samples were collected at 0 hour (just prior to dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 24 hours after dosing. For Regimen D (Avelox), samples were collected at 0 hour (just prior to dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours after dosing.

o Any SAEs occurring after the informed consent/HIPAA authorization form was signed and dated were collected. Nonserious adverse events were collected as medical history from the time the informed consent/HIPAA form was signed until the first dose of study drug was administered on Day 1 of Period 1.

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/s/

Joanne Zhang

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Clinical Reviewer for this Study Report was Dr. Suchitra
Balakrishnan.

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8/13/2008 01:53:08 PM

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